“COMPARISON OF VARIOUS IMAGING MODALITIES FOR TARGET VOLUME DELINEATION, TREATMENT RESPONSE ASSESSMENT USING PERCIST CRITERIA AND PROGNOSTICATION ALGORITHM FOR PREDICTING REPONSE TO TREATMENT IN HEAD AND NECK CANCERS”

DEPARTMENT OF RADIATION ONCOLOGY

CHRISTIAN MEDICAL COLLEGE

VELLORE, TAMIL NADU

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

MD – RADIATION ONCOLOGY (BRANCH IX)

EXAMINATION MAY 2019

TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI 600032

CERTIFICATE

This is to certify that the dissertation entitled "COMPARISON OF VARIOUS IMAGING MODALITIES FOR TARGET VOLUME DELINEATION, TREATMENT RESPONSE ASSESSMENT USING PERCIST CRITERIA AND PROGNOSTICATION ALGORITHM FOR PREDICTING RESPONSE TO TREATMENT IN HEAD AND NECK CANCER" is a bonafide work done by Dr. GOUTHAM SUNNY, Post Graduate Student in the Department of Radiation Oncology, Christian Medical College, Vellore during the period from April 2016 to April 2019 and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfilment of the MD Branch IX Radiation Oncology examination conducted in May 2019.

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I, Goutham Sunny, PG Registrar, Department of Radiation Oncology, Christian Medical College Vellore hereby declare that the dissertation titled "COMPARISON OF VARIOUS IMAGING MODALITIES FOR TARGET VOLUME DELINEATION, TREATMENT RESPONSE ASSESSMENT USING PERCIST CRITERIA AND PROGNOSTICATION ALGORITHM FOR PREDICTING RESPONSE TO TREATMENT IN HEAD AND NECK CANCER" is a bonafide work done by me for partial fulfilment towards MD Radiation Oncology (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in May 2019

Dr. Goutham Sunny

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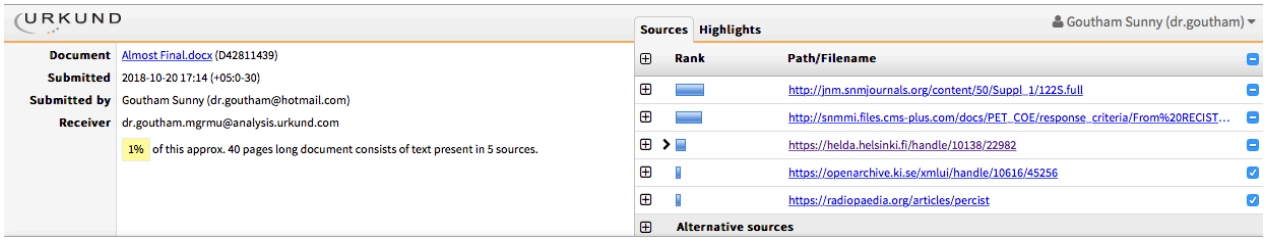
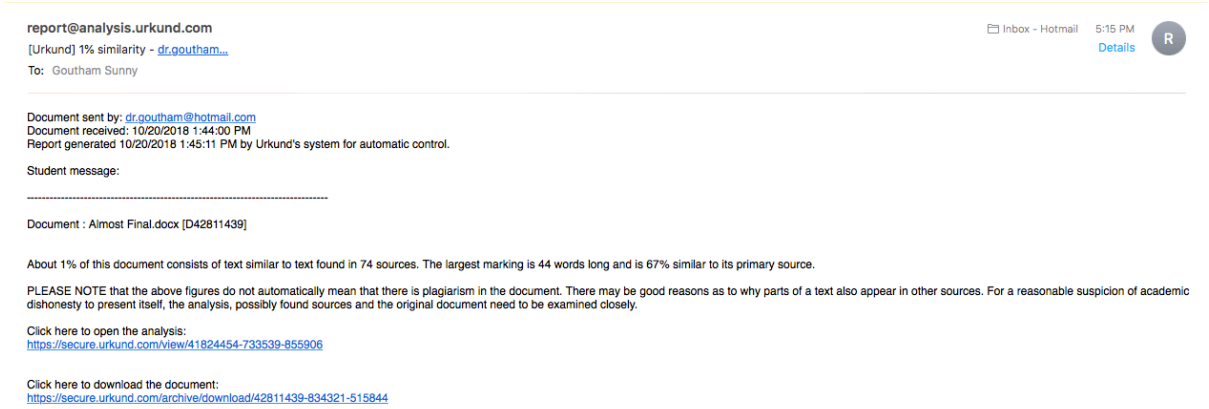
PLAGIARISM CHECK





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Comparison of various imaging modalities for target volume delineation, treatment response assessment using PERCIST criteria and prognostication algorithm for predicting response to treatment in Head and Neck cancers.
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Dear Dr. Goutham Sunny,
I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
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Institutional Review Board

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Dear Dr. Goutham Sunny,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Comparison of various imaging modalities for target volume delineation, treatment response assessment using PERCIST criteria and prognostication algorithm for predicting response to treatment in Head and Neck cancers" on September 05th 2016.

The Committee reviewed the following documents:

1. IRB Application format
2. Informed Consent and Information Sheet
3. Cvs of Drs. Subhashini, Rajesh I, Rajesh B, Paul Ravindran, Henry Finlay, David Mathew, Devakumar, Aparna, Rajiv M, Rajan Sundaresan, Rita Ruby, Suma Susan.
4. No. of documents 1 – 3

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The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on September 05th 2016 in the C K Job Hall, Paul Brand Building, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC,Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist &Epidemiologist
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Sheela Durai	MSc Nursing	Professor, Medical Surgical Nursing, CMC, Vellore	Internal, Nurse
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Rajesh Kannangai	MD, PhD.	Professor, Clinical Virology, CMC, Vellore	Internal, Clinician

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Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC, Vellore	Internal, Clinician
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS, MCh	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Comparison of various imaging modalities for target volume delineation, treatment response assessment using PERCIST criteria and prognostication algorithm for predicting response to treatment in Head and Neck cancers" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:
A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty Thousand only) each will be released at the end of the first year as 2 nd Installment.

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
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I would like thank my co guides, Dr. Manu Mathew, Dr. Rajesh B, Dr David Mathew, Dr. Paul Ravindran, Dr. Henry Finlay Godson, Dr. Aparna I, Dr Rajiv Micheal, Dr. Rajan Sundaresan, Dr Rita Ruby and Dr. Suma Susan. Without their help, the completion of this work would have been immeasurably more difficult.

I would like to thank my patients who consented and were part of this study for contributing their extra bit towards science in the midst of their hardships and enabled research to happen.

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LIST OF ABBREVIATIONS USED

HPV Human papilloma virus

IJV Internal jugular vein

CUP Carcinoma unknown primary

WHO World health organisation

ICMR Indian council of medical research

NRCP National cancer registry program

UV Ultraviolet

SCC Squamous cell carcinoma

GTV Gross tumor volume

CTV Clinical target volume

PTV Planning target volume

OAR Organ at risk

USG Ultrasonography

CT computed tomography

MRI Magnetic resonance imaging

PET Positron emission tomography

FDG Fluorodeoxyglucose

IV Intravenous

NPL Nasopharyngolaryngeal

RECIST Response evaluation criteria in solid tumors

PERCIST Positron emission tomography response criteria in solid tumors

SUV Standardized uptake value

SUL SUV normalized to lean body mass

MTV Metabolic tumor volume

TLG Total lesion glycolysis

CMR Complete metabolic response

PMR Partial metabolic response

SMD Stable metabolic disease

PMD Progressive metabolic disease

CR Complete response

PR Partial response

SD Stable disease

PD Progressive disease

RTOG radiation therapy oncology group

ECOG Eastern cooperative oncology group

SWOG Southwest oncology group

EORTC European organization for research and treatment of Cancer

IMRT Intensity modulated radiation therapy

SEER Surveillance, Epidemiology and End result program

VMAT Volumetric arc therapy

NTCP Normal tissue complication probability

TCP Tumor control probability

MU Monitor units

EGFR Epidermal growth factor receptor

SBR Source or signal to background ratio

LFFS Local failure free survival

DMFS Distant metastasis free survival

PFS Progression free survival

DFS Disease free survival

LC Local control

OS Overall survival

BED Biological equivalent dose

VOI Volume of interest

ROI Region of interest

ABSTRACT

OBJECTIVE

To compare tumour volumes created using F 18 FDG PET CT scan before starting treatment and after completion of chemo radiation/radical radiotherapy to assess treatment response using PERCIST criteria in Head and Neck cancers and to create a prognostication algorithm to predict treatment response.

METHODS

This was a prospective cross-sectional study done in the Department of Radiation Oncology at Christian Medical College, Vellore. Patients with squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and laryngopharynx planned for radical irradiation with or without concurrent systemic treatment were recruited and underwent a PET CT scan in planning position. These patients underwent a response assessment PET CT 12 weeks following treatment. Baseline diagnostic and staging advantage of PET CT, its role in RT planning, PET CT biomarkers were analysed. Response assessment was done by clinical examination and NPL scopy, RECIST and PERCIST and response assessment was analysed.

RESULTS

PET CT was beneficial in diagnosis, staging and detection of metastatic disease. It was useful in delineation of tumor volume and reduction in volumes. Baseline TLG was a good predictive biomarker with a low baseline value suggestive of good response to treatment. PERCIST calculated using change in

SUL had good correlation with response. The patients who had complete metabolic response had a high negative predictive value suggestive of absence of disease. PET CT helped to differentiate abnormal scopy findings from diseased scopy by assessing decline in SUL value. PERCIST PMR patients with a normal scopy and complete response in RECIST had a significant drop in SUL, TLG and SUVmax compared to stable and progressive metabolic response. Change in TLG was a good marker to prognosticate response to treatment. Change in MTV was a prior biomarker to assess response.

CONCLUSION

PET CT was of use in diagnosis, staging, RT planning and response assessment. Baseline TLG was the best biomarker to prognosticate response to treatment. PERCIST SUL was the best way to assess response.

AIM

Comparison of tumour volumes created using F 18 FDG PET CT scan before starting treatment and after completion of chemo radiation/radical radiotherapy to assess treatment response using PERCIST criteria in Head and Neck cancers and to create a prognostication algorithm to predict treatment response.

OBJECTIVES

Primary Objective

- To compare tumour volumes using PET CT before starting and after completion of treatment to assess treatment response using PERCIST criteria.

Secondary Objective

- Evaluate the changes in target volume and staging due to addition of PET to CT and MRI
- To compare metabolic volumes created using PET with anatomic volume created using CT and MRI
- To create a prognostication algorithm for response prediction using PERCIST
- To look at whether there is any association between the aggressiveness of the tumour and metabolic data obtained in the PET

INTRODUCTION

Intensity Modulated Radiation Therapy (IMRT), is presently considered the standard of care in managing head and neck malignancies. With the use of IMRT the dose to the primary tumor can be escalated while keeping the dose to the adjacent normal structures at the minimum. Precise delineation of target volume and organs at risk is required for planning purpose. Conventionally Radiation Oncologist utilize CT and MRI to delineate the gross tumour volumes. Anato-metabolic imaging using 18F-fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is used in the diagnosis, initial staging, and response assessment in various malignant tumors with high diagnostic accuracy. The advantages of PET/CT in radiotherapy planning is that it improves tumor delineation, reducing intra-observer and inter-observer variability and making treatment volumes more standard across individuals and institutions.

This research work will be carried out on head and neck cancer patients (oral cavity, oropharynx, hypopharynx and larynx) undergoing radiation therapy by intensity modulated radiation therapy with planning PET CT. In this study, the eligible patients planned for treatment with IMRT will be prospectively recruited from December 2016 to Aug 2018 and will undergo a planning PET CT. The PET CT will be taken in the treatment position with head and neck ray cast. In the PET CT image, metabolic tumour volume and gross/anatomic tumour volume will be delineated after discussion

with radiologist and nuclear medicine consultant according to current guidelines. Comparison of the volumes will be done and patients will be treated according to tumour volume based GTV. PET CT data will also be used to assess if there is any change in staging when compared to CT scan based staging.

The patient will be followed up 3months after treatment completion with PET CT and comparison of pre and post treatment tumour volumes will be done and treatment response will be assessed using PERCIST criteria and also will create a prognostication algorithm to predict treatment response.

Study will also assess the impact of PET scan on staging – change in nodal staging, primary tumour volume, identifying synchronous malignancies and metastases.

ANATOMY

Head and neck squamous cell carcinomas originate from the mucosa of the following anatomic locations, namely the nasopharynx, the oral cavity, the oropharynx, the hypopharynx and the larynx. The need to identify these critical areas and its boundaries is to identify the site of origin so as tailor treatment as it varies for various subsites and has significant role in the choice of management modality, treatment options, prognosis and survival.(1)

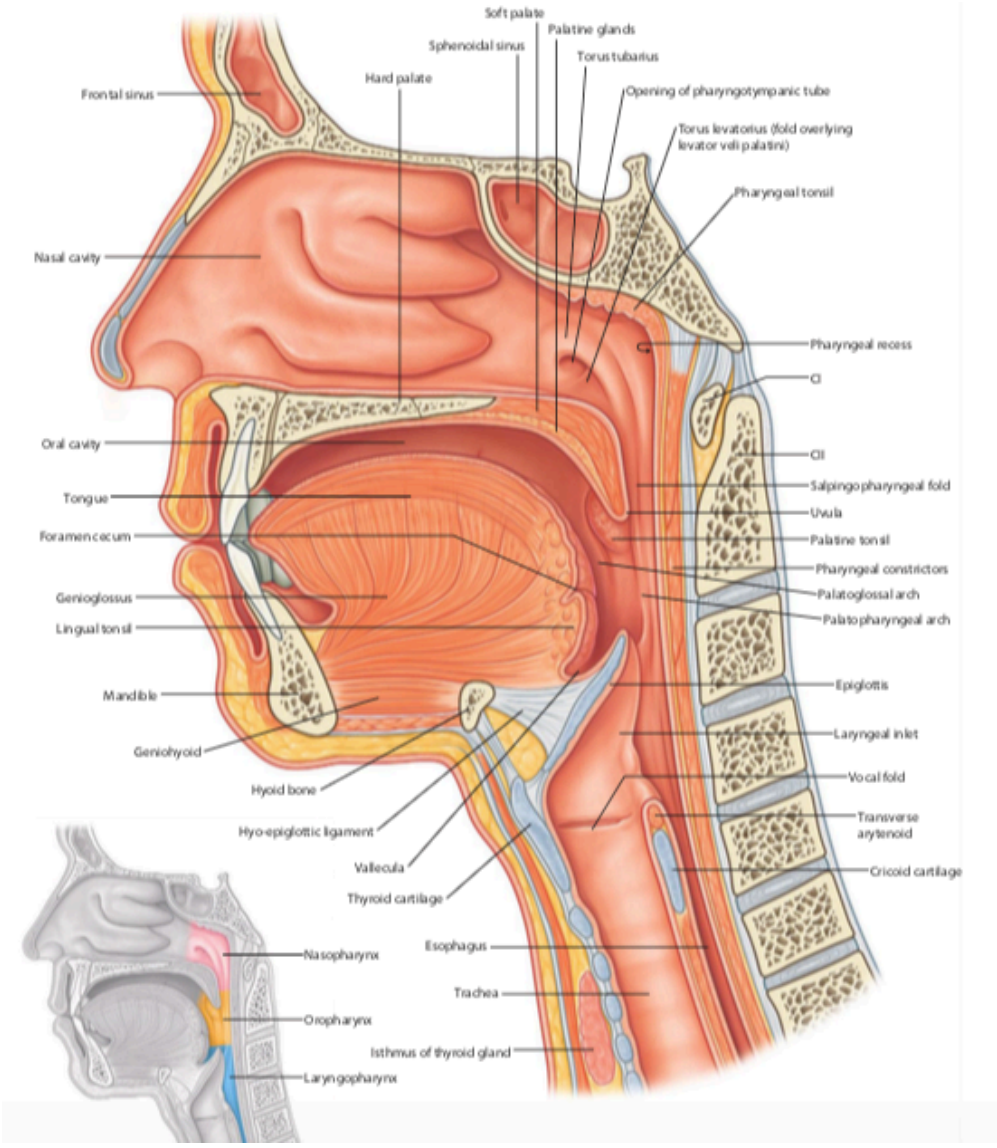

Figure 1. Sagittal section - Anatomy of head and neck

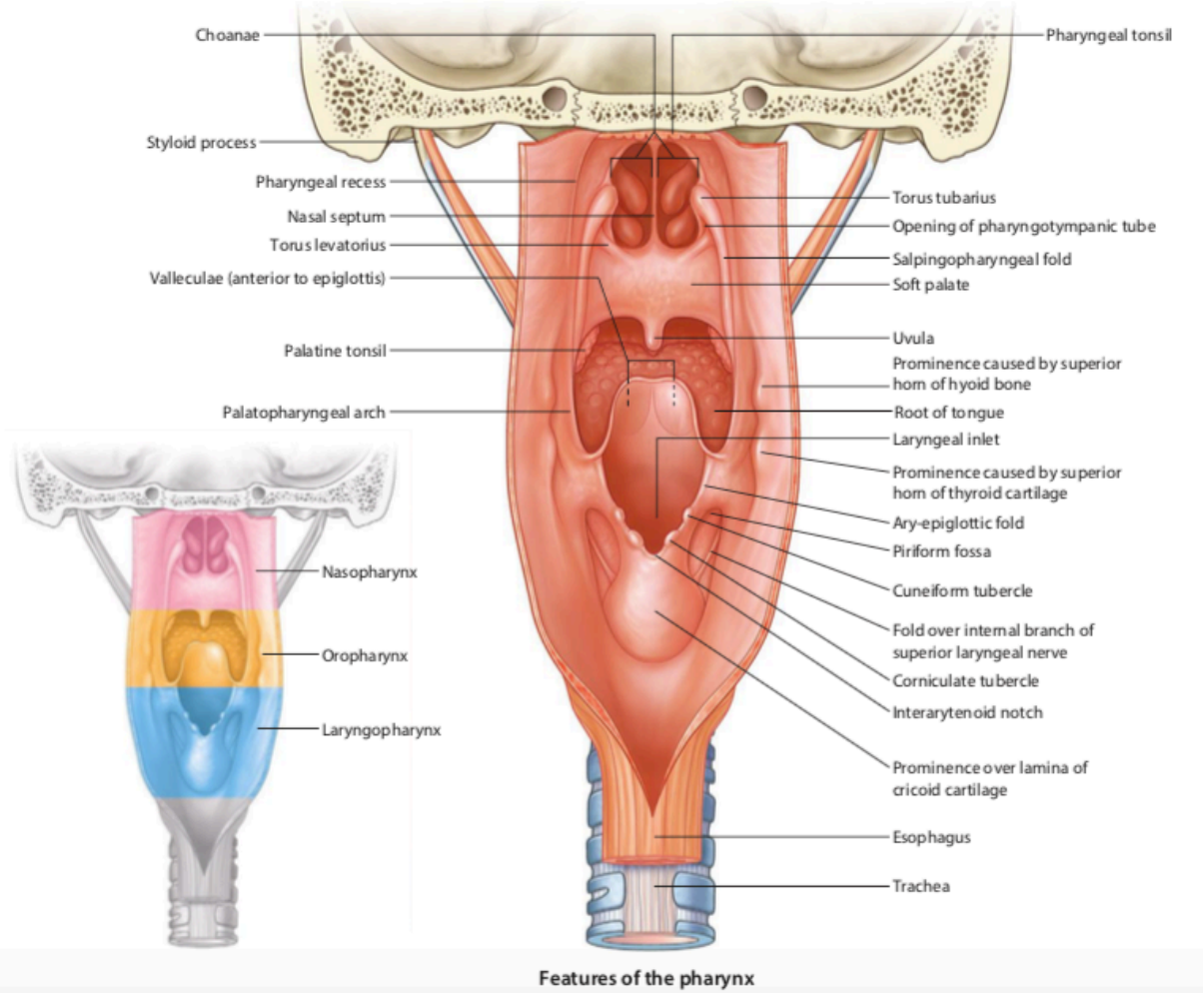

Figure 2 Coronal section - Anatomy of pharynx

Oral Cavity

The intersection between the vermillion (red lip) and skin forms the anterior border of the oral cavity, laterally, buccal mucosa or the cheek forms its walls, the posterior limit is the junction between soft and hard palate superiorly and inferiorly it is the circumvallate papillae of the tongue which forms a V-shaped line. The various subsites in the oral cavity are

1. Upper and lower lip

2. Buccal Mucosa
3. Lower alveolar ridge
4. Upper alveolar ridge
5. Retromolar trigone
6. Floor of mouth
7. Hard palate
8. Oral Tongue

It is critical to understand these subsites and the boundaries, especially the posterior boundary to differentiate between an oral cavity and oropharyngeal primary.

Oropharynx

The intersection between the hard and soft palate forms the anterior boundary of oropharynx superiorly and inferiorly it is formed by the circumvallate papillae of the tongue, an imaginary horizontal plane through the soft palate separates it from the nasopharynx superiorly and inferiorly, a similar horizontal plane through the hyoid separates it from the hypopharynx. The various oropharyngeal subsites are

1. Palatine Tonsils
2. Base of Tongue
3. Oral surface of soft palate and Uvula
4. Posterior pharyngeal wall
5. Lateral pharyngeal wall
6. Anterior and Posterior tonsillar pillar mucosa

7. Glossotonsillar Sulcus

Human Papilloma Virus associated squamous cell carcinoma of the oropharynx most commonly originates from the lymphoid tissue of lingual and palatine tonsils.(2)

Hypopharynx

An imaginary horizontal plane through the hyoid bone separates hypopharynx from the oropharynx superiorly and another imaginary horizontal plane through the cricoid cartilage sets the lower limit of hypopharynx. The various anatomical subsites are

1. Pyriform Sinus
2. Lateral pharyngeal wall
3. Posterior pharyngeal wall
4. Post-cricoid region

Larynx

Larynx or the voice box is a complex structure that can be further sub classified into three separate regions; the supraglottic larynx, glottic larynx and subglottic larynx. The superior extent of supraglottic larynx is lingual surface of epiglottis and the inferior extent is the laryngeal ventricle just above true vocal folds. The junction between the base of tongue and lingual surface of epiglottis is the vallecula.

The subsites of supraglottic larynx are

1. Suprahyoid epiglottis

2. Infrahyoid epiglottis
3. Laryngeal surface of aryepiglottic folds
4. Arytenoids
5. False vocal folds and ventricles

The subsites of glottic larynx are

1. Anterior commissure
2. Posterior commissure
3. True vocal folds

The subglottic larynx is a space below the true vocal folds with an imaginary horizontal plane through the inferior border of cricoid cartilage as lower limit. (2)

The four layers of the pharynx from within outwards are

Mucous membrane that continues with the eustachian tubes and the nasal, oral and laryngeal cavities

Fibrous coat that is the thickest in the superior part and forms a median raphe in the posterior aspect

Muscular coat formed by 2 layers of muscular tissue – external constrictors and internal levators

Fascial coat (Buccopharyngeal fascia)

Lymphatics of the Head and Neck

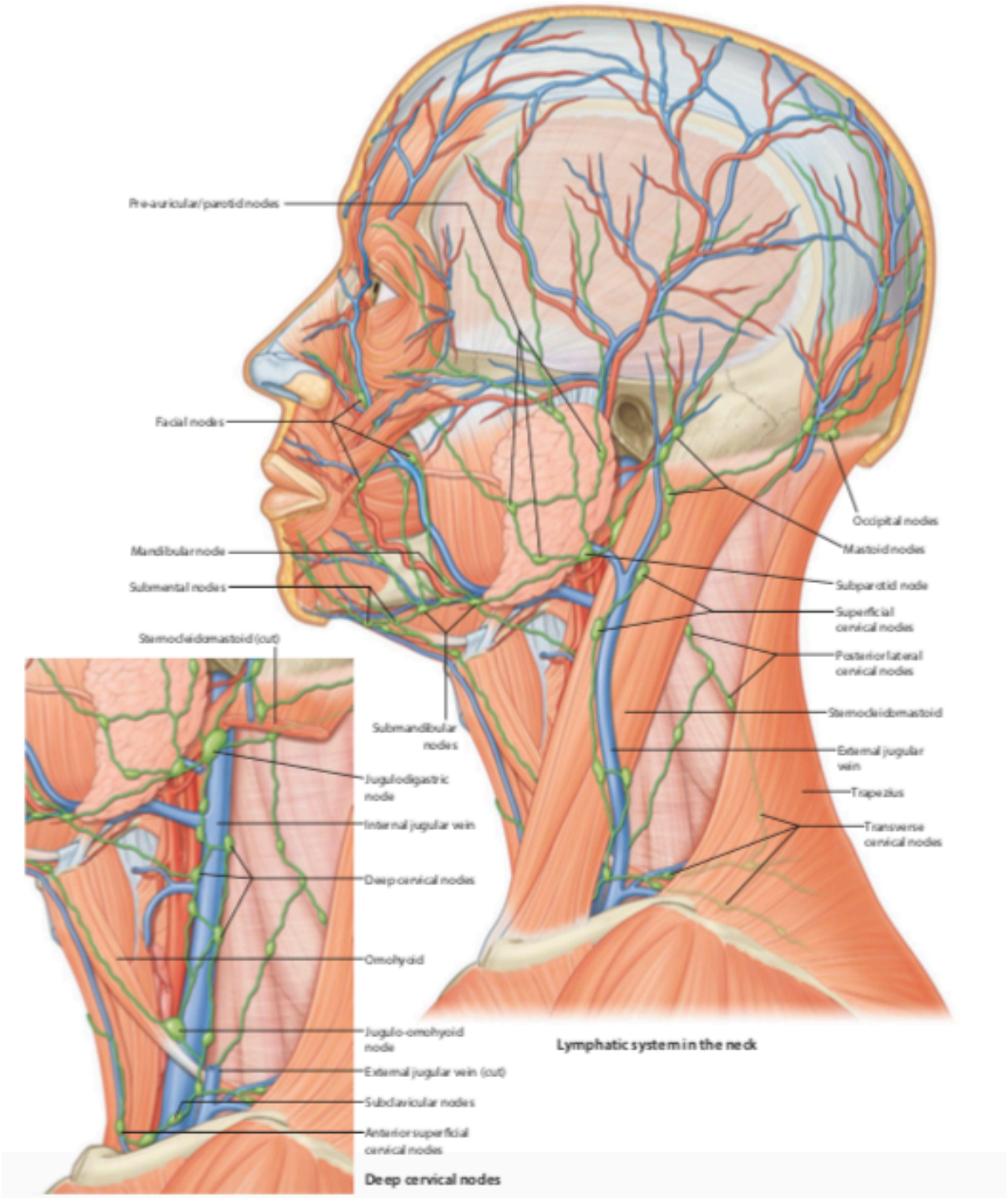

Figure 3 Lymphatics of neck

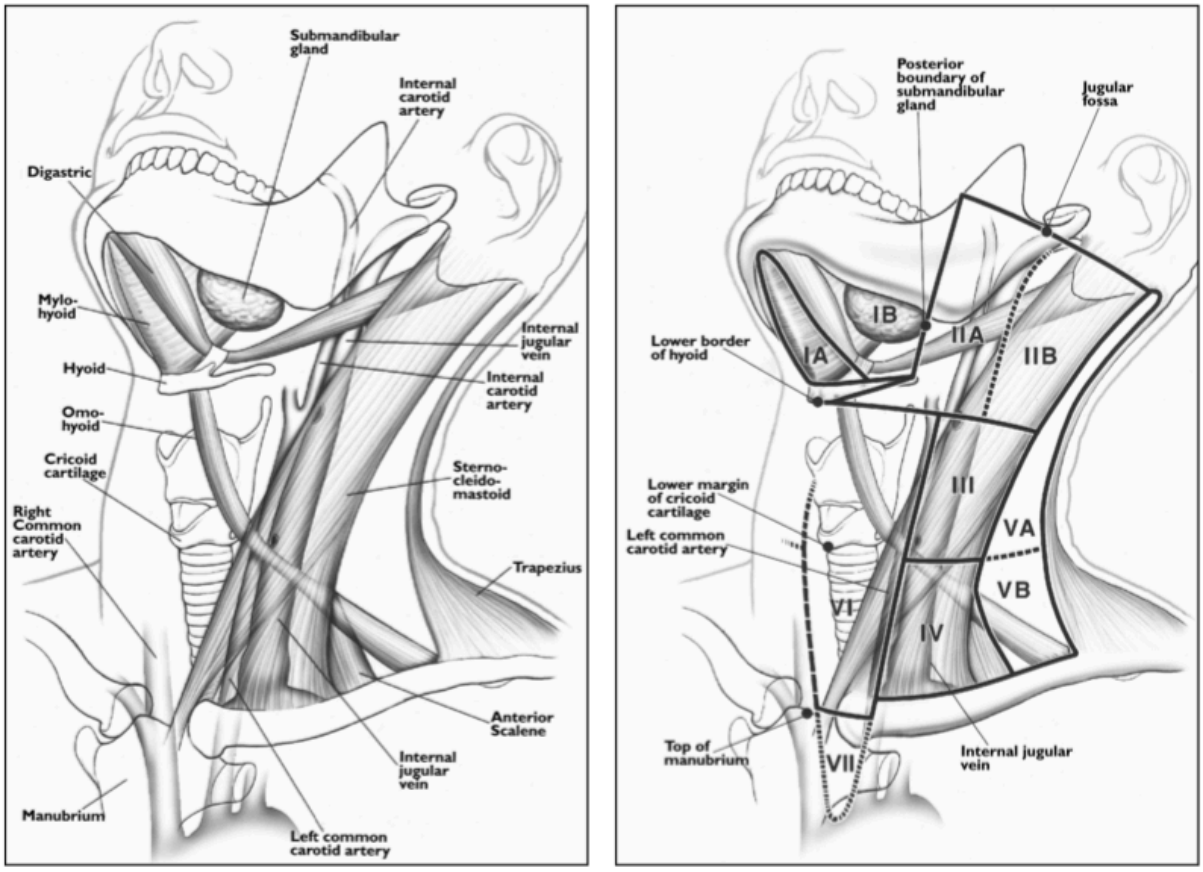

Figure 4 A. Drawing shows anatomy pertinent to nodal classification. B, Drawing shows specific margins of anatomy seen in A that relate to definitions of classification levels (3).

Level Ia

The location of level Ia nodes is the median region between the anterior bellies of the digastric muscles

It drains the skin of the chin, mid and lower lip, tip of tongue and the anterior part of floor of mouth.

Highest risk of nodal metastasis to level Ia region is floor of mouth, anterior part of oral tongue, anterior mandibular alveolar ridge and lower part of lip.

Level Ib

The location of Level Ib nodes is the space between inner aspect of mandible laterally and digastric muscles medially. It extends anteriorly up to symphysis menti and posteriorly up to submandibular glands.

It drains the Level Ia, lower part of nasal cavity, soft and hard palate, mandibular and maxillary ridges, cheek, the upper and lower lips and the anterior tongue.

Highest risk of nodal metastasis to Level Ib is from malignancy of oral cavity, anterior nasal cavity, soft tissue structures of the middle of the face and submandibular gland.

Level II

Level II is also known as the upper jugular nodes and its location is around the upper one third of internal jugular vein and upper spinal accessory nerve. It lies between medial surface of sternocleidomastoid muscle laterally and the internal carotid and scalenius muscle medially from the lateral process of first cervical vertebrae to the caudal edge of hyoid bone. It is further subdivided into Level IIa and IIb by the posterior edge of internal jugular vein.

It drains face, parotid gland and the submandibular, submental and retropharyngeal lymph nodes. It also drains the nasal cavity, pharynx, larynx, external auditory canal, middle ear, sublingual and submandibular salivary glands.

Highest risk of nodal metastasis to level II is from malignancy of nasal cavity, oral cavity, nasopharynx, oropharynx, hypopharynx, oropharynx, larynx and major salivary glands.

Level III

Level III is also known as the middle jugular nodes and is located around the middle third of the IJV. It is the inferior extension of Level II. Its superior margin is caudal edge of the body of hyoid bone and extends inferiorly till the caudal edge of cricoid cartilage. Anteriorly it extends till anterior edge of sternocleidomastoid or posterior one third of thyrohyoid muscle and posteriorly the posterior edge of sternocleidomastoid. Laterally it is limited by deep surface of sternocleidomastoid and medially the medial edge of common carotid artery and scalenius muscle.

It drains the base of tongue, tonsils, larynx, hypopharynx and thyroid gland. It also receives lymphatics from the level II, V, retropharyngeal, pretracheal and recurrent laryngeal nodes.

Highest risk of nodal metastasis to Level III is from the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx.

Level IV

Level IVa is also known as the lower jugular nodes and is located around the lower third of the IJV. It is the inferior extension of Level III nodes and extends to a limit set arbitrarily as 2 cm above the sternoclavicular joint. Its anterior extent is the anterior edge of the sternocleidomastoid muscle superiorly and body of sternocleidomastoid muscle inferiorly. Its posterior extent is posterior edge of sternocleidomastoid muscle superiorly and scalenius muscle inferiorly. Laterally it is limited by medial border of sternocleidomastoid superiorly and lateral border of the muscle inferiorly. Its medial

margin is medial border of common carotid artery, medial margin of thyroid gland and scalenius muscle and medial border of sternocleidomastoid in the inferior aspect.

It drains the larynx, hypopharynx and thyroid gland and also received efferent from level III and V, recurrent laryngeal, pretracheal and retropharyngeal nodes.

Level IVb is also known as the medial supraclavicular nodes. It located in continuation of Level Iva and extends down to the superior edge of manubrium sternum. Its anterior extent is the deep surface of sternocleidomastoid muscle. Superiorly the posterior extent is anterior border of scaleneus muscle and inferiorly it is formed by apex of lung, brachiocephalic vein and artery, common carotid artery, subclavian artery. The medial extent is level VI and medial edge of common carotid while lateral limit is lateral edge of scaleneus muscle.

It drains the esophagus, larynx, hypopharynx, trachea and thyroid gland and receives efferent lymphatics from Level Iva, Vc, recurrent laryngeal nodes and pretracheal nodes.

Level V

Level V nodes are also known as posterior triangle nodes and it is located posterior to the sternocleidomastoid muscle. It is located around the inferior part of spinal accessory nerve and the transverse cervical vessels. The superior extent is an imaginary horizontal plane drawn at the level of cranial edge of hyoid bone and inferiorly an imaginary plane crossing transverse cervical vessels. The lateral extent is platysma muscle and skin and medially in the superior aspect it is the levator scapulae and inferior aspect by posterior scaleneus muscles. The posterior margin is the limit

set at anterior border of the trapezius muscles. It is further subdivided into level Va and Vb by the caudal edge of cricoid cartilage.

It drains the parietal and occipital scalp, skin of lateral and posterior neck and shoulder, oropharynx, nasopharynx, thyroid gland and efferent lymphatics from retroauricular and occipital nodes.

Highest risk of nodal metastasis to level V is from malignancies of the nasopharynx, oropharynx and thyroid gland.

Level Vc is the lateral supraclavicular nodes which are located in continuation with the posterior triangle nodes (Level Va and Vb) from the transverse cervical vessels down to an arbitrarily set limit of 2 cms superior to manubrium sternum.

Level VI nodes are also known as the anterior compartment nodes. Superficially it is called as the anterior jugular nodes (Level VIa) and in the deep previsceral space, pre-tracheal, pre-laryngeal and para-tracheal (recurrent laryngeal nerve) nodes (Level VIb).

Level VIIa

Leve VIIa nodes are also called as the retropharyngeal nodes. It extends superiorly from the upper edge of first cervical vertebrae to cranial edge of body of hyoid inferiorly. Its anterior margin is formed by the pharyngeal constrictor muscles and posteriorly by the longus capitus and longus colli muscles. It is bounded on the lateral margin by the medial edge of internal carotid artery.

It drains the oropharynx, nasopharynx, posterior pharyngeal wall and Eustachian tube.

The other nodal groups which have been described are the Level VIIb which is known as retro-styloid nodes, level VIII which are known as the parotid nodes, Level IX which are known as the bucco-facial and Malar nodes, Level Xa which are known as the retroauricular nodes and the Level Xb which are known as the occipital group of nodes.(4)

EPIDEMIOLOGY

Head and Neck cancers are the sixth most prevalent cancer world over. Statistics estimate about 6.3 lakh patients are newly diagnosed yearly which leads to 3.5 lakh deaths annually. (5) More than 90% of all head and neck cancers diagnosed comprise of squamous cell carcinoma. The worldwide distribution of squamous cell carcinoma of the head and neck shows great variation and various demographic variation in tobacco and alcohol consumption could be attributed as the main cause for this.

The WHO GLOBOCAN Report 2012 also showed a very high 5-year prevalence rates for head and neck cancers in India. The 5-year prevalence rate of lip and oral cavity was 12.6%, while for Laryngeal cancers it was 6.8%, nasopharynx 1.1% and oropharynx 7%. This clearly points out the high burden of head and neck cancers in India with 5-year prevalence rates of nearly 27% (6)

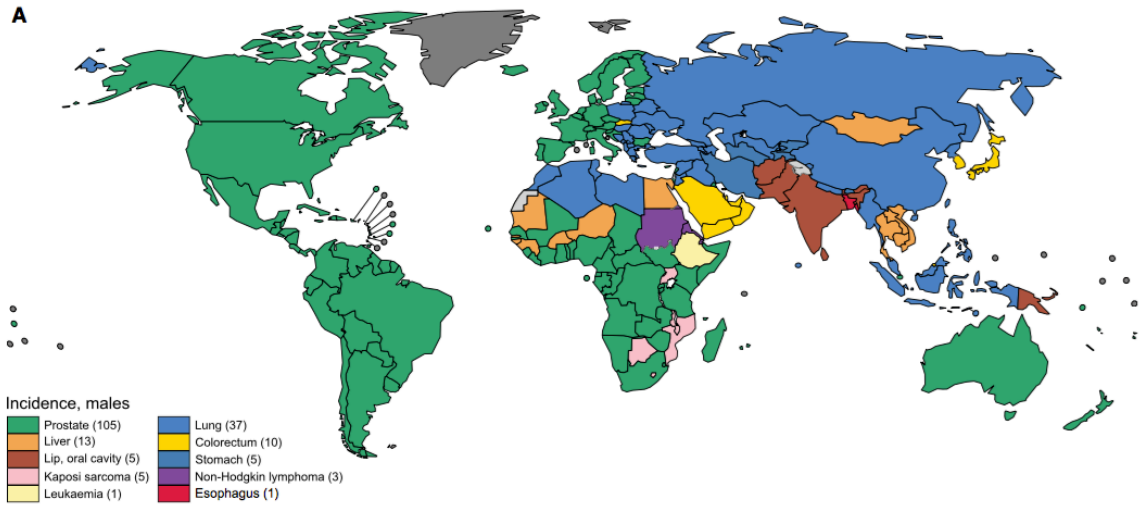

Figure 5 GLOBOCAN worldwide incidence of malignancies - site wise

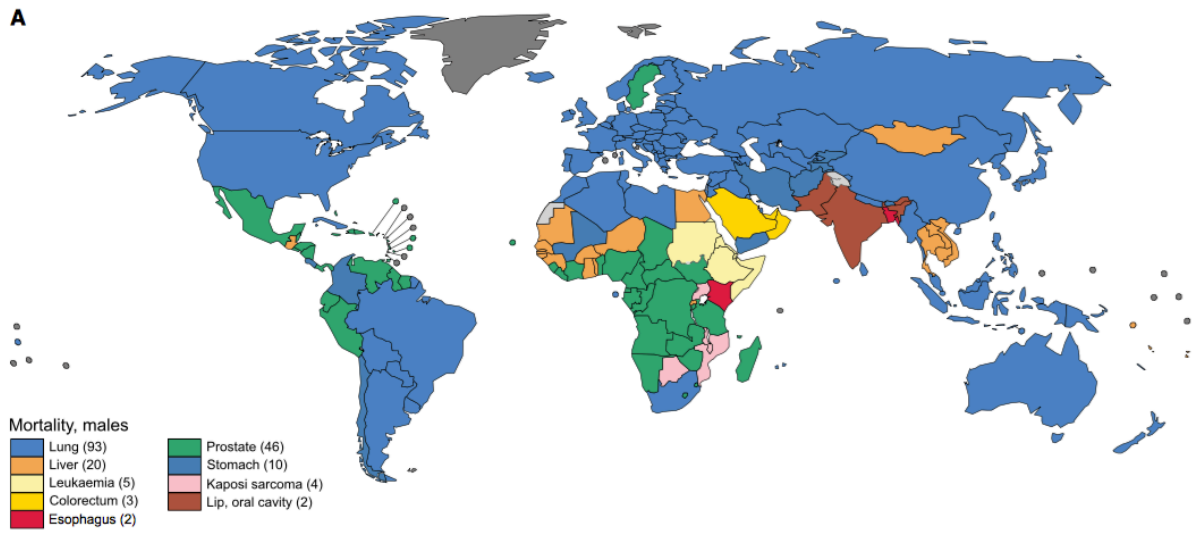

Figure 6 GLOBOCAN worldwide mortality of malignancies - site wise

GLOBOCAN data on incidence and mortality 2018 (7)

The decreasing incidence of oropharyngeal squamous cell carcinoma and laryngeal squamous cell carcinoma in the US and other developed nations has been attributed to the decreased use of tobacco products and smoking. Meanwhile there is an increasing trend of oropharyngeal squamous cell carcinomas in these regions which are associated with high risk subtypes of human papilloma virus. (8)

Four decades ago the incidence of HPV associated carcinomas of the oropharynx was about 16% but currently it stands at about 75%. The HPV associated head and neck squamous cell carcinoma has been attributed to more than 25% increase in the incidence of head and neck squamous cell carcinoma in the united states in the last 10 years. (9) HPV associated oropharyngeal squamous cell carcinoma has been recognized as a unique subset due to its unique etiology, molecular pathogenesis, clinical presentation and response to treatment.(10)(11)

The Indian Council of Medical Research (ICMR) started the National Cancer Registry Program (NCRP) in 1981. (12) There are 28 cancer registries located throughout India and these are hospital based and population based registries. Head and neck squamous cell carcinomas accounted for about 30% of all cancers in males. The most common cancer was the oral cavity and tongue followed by pharyngeal cancers. The reason for the high incidence of oral cavity cancers is estimated to be due to tobacco use which is discussed in the following section. (13)

ETIOLOGY

The factors that contribute to development of squamous cell carcinoma of head and neck includes diet, habits, geographical location and genetic background. The most important of the above-mentioned side effects are tobacco use and alcohol consumption and these both have shown to have a synergistic effect. (14) Human Papilloma Virus infection with high risk sub-types (16,18,31 and 33) play a major causal role in the development of oropharyngeal squamous cell carcinoma with very typical clinical and molecular features. This subset of oropharyngeal squamous cell carcinoma associated with HPV has been linked to an improved outcome and survival. (15) But when it has developed in a person with concurrent tobacco habit the survival benefit doesn't seem to be significant. Other contributing factors for head and neck squamous cell carcinoma are chronic exposure to sun light or UV radiation for SCC of lips, iatrogenic immunosuppression following solid organ transplant, family history of head and neck squamous cell carcinoma, diseases like Plummer-Vinson syndrome, Fanconi anemia and dyskeratosis congenita, diets deficient in anti-oxidants and older age.(10)(16)

The Precursor lesions and conditions of Head and neck squamous cell carcinoma are

Leukoplakia – white patch or plaque that cannot be rubbed off and cannot be characterized histopathologically or clinically to any specific disease

Figure 7 Leukoplakia

Progressive verrucous leukoplakia – multifocal, proliferative and progressive form of leukoplakia which usually begins as simple keratosis and becomes verrucous and multifocal involving large contiguous sites.

Figure 8 Progressive verrucous leukoplakia

Erythroplakia – well defined, raised, velvety plaque that cannot be clinically characterized as any other disease.

Figure 9 Erythroplakia

Oral submucous fibrosis – chronic and progressive condition characterized by diffuse mucosal rigidity. It occurs due to dense fibrosis within the lamina propria that may extend to underlying skeletal muscle.

Figure 10 Oral submucous fibrosis

Oral lichen planus – most common autoimmune chronic auto inflammatory disorder of the mucosa of oral cavity that can affect about 1-2% of all adults in the middle age.(10)

Figure 11 Oral Lichen Planus

HISTOLOGY - HEAD AND NECK SQUAMOUS CELL CARCINOMA

1. Conventional/ keratinizing – Majority of all squamous cell carcinomas in the head and neck found outside the oro and nasopharynx belong to this subtype. The grading of conventional SCC is based on cytological maturation, extent of keratinization and the growth pattern into well, moderately and poorly differentiated squamous cell carcinoma. The use of tobacco and or alcohol most commonly leads to this particular subtype of SCC. (17)

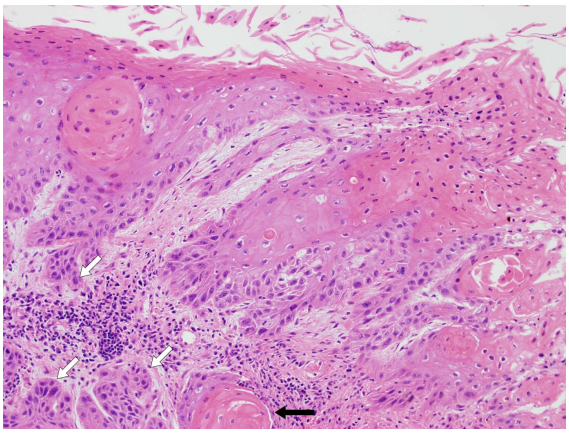

Figure 12 Keratinizing squamous cell carcinoma

2. HPV associated SCC – They are more monotonous in appearance with limited keratinization compared to the conventional subtype. The most distinct morphological feature of this type of SCC also applies to lymph nodal metastasis if any. They are most often cystic by imaging and on histology can appear like branchial cleft cyst or carcinoma.

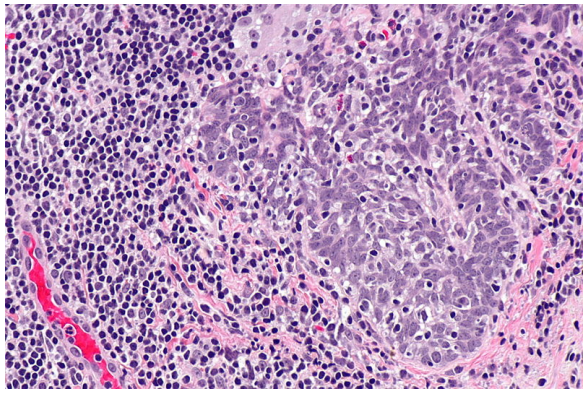

Figure 13 HPV associated squamous cell carcinoma

3. Veruccous SCC – Locally aggressive subtype that shows a broad pushing growth downwards and has an exophytic warty appearance. Histologically the cells are bland with minimal alteration. Since they do not usually metastasize, it has to be differentiated from the more aggressive hybrid or conventional SCC. Complete evaluation of these lesions requires full excision with adjacent normal mucosa.

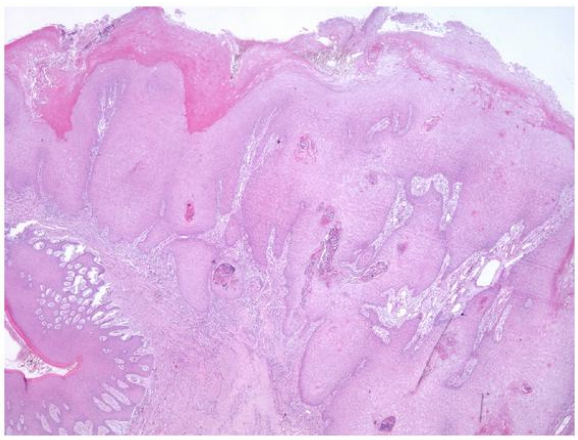

Figure 14 Verrucous squamous cell carcinoma

4. Papillary SCC – Rare subtype seen more commonly in the nasal cavity and larynx. Histologically they have long papillary fronds lined by neoplastic cells without keratinization overlying fibrovascular cone. Its confirmation

requires clinical correlation as determination of invasion is difficult on biopsies due to little underlying stroma.

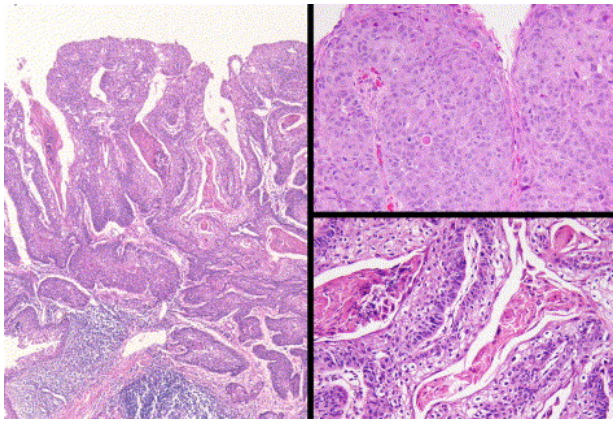

Figure 15 Papillary squamous cell carcinoma

5. Basaloid SCC – High grade histological variant that overlaps between solid adenoid cystic carcinoma and neuroendocrine carcinomas morphologically. It often requites immunohistochemical confirmation. This variant arising in the oropharynx is commonly associated with HPV but not at other sites. (18)

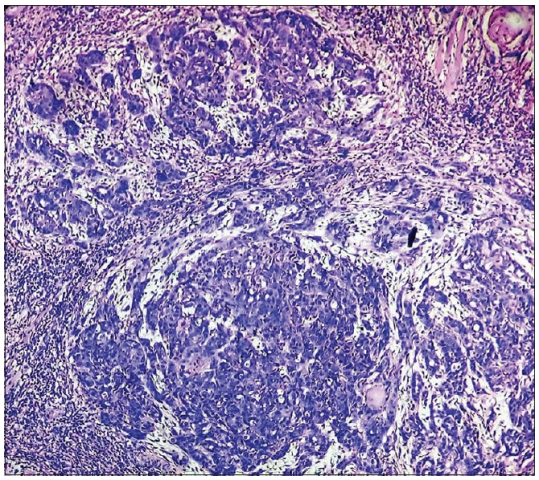

Figure 16 Basaloid squamous cell carcinoma

6. Sarcomatoid SCC – also called as spindle cell carcinoma, it is a high-grade tumor that grows in sheets composed of pleomorphic spindle shaped cells

which exhibit frequent mitosis and may grow as an exophytic or polypoid mass. (19)

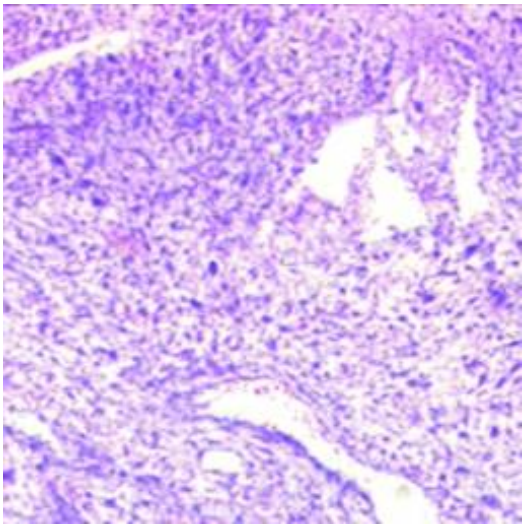

Figure 17 Sarcomatous squamous cell carcinoma

IMAGING IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

To visualize tumors located in the mucosa of upper aero digestive tract both clinical examination and endoscopy are usually adequate. But all areas are not well visualized by these methods and in addition imaging is necessary to visualize submucosal and deeper tumors and to evaluate the loco-regional extent of tumors. The role of imaging is as follows

Detection or exclusion of tumors

If present to identify its extent and delineate its size

Identify adjoining structures affected

Identify spread to lymph nodes

Identify perineural or perivascular spread

Identify bony invasion

Detect distant metastasis

Stage the tumor with all the available information

It can also be used for identifying tissue for targeted biopsy, for planning radiation therapy, for adaption during radiation therapy, to evaluate response to treatment after completion of treatment, to identify recurrence while on follow up to offer salvage to improve clinical outcome. It should also be able to identify synchronous primaries or second primary malignancy that is common in head and neck region due to field cancerization due to the etiological agents responsible.

The imaging modalities available include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography with CT (PET – CT).(20)

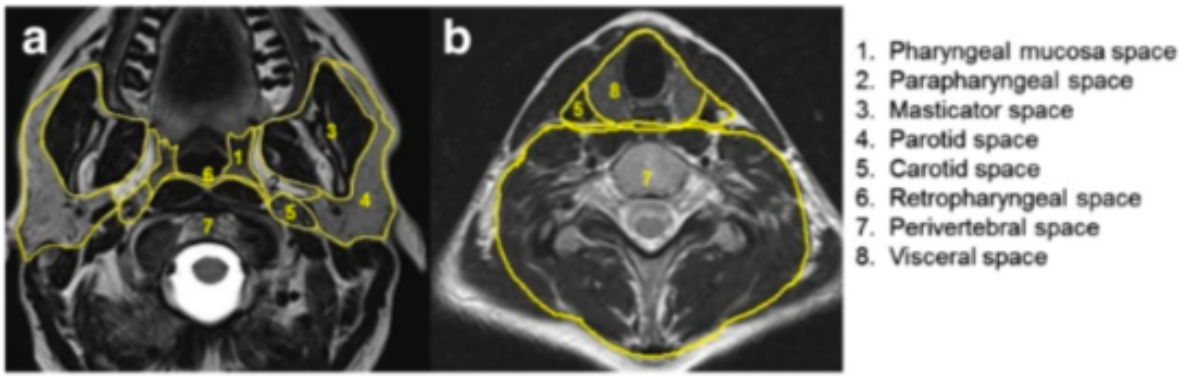

Figure 18 Spaces in head and neck – cross sectional CT image

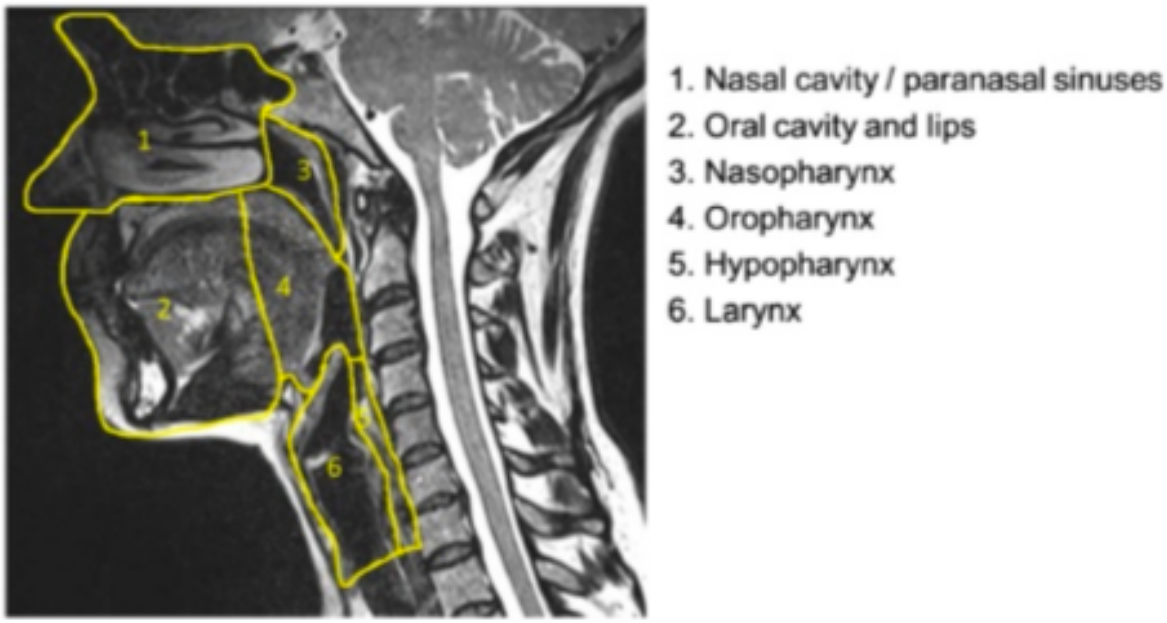

Figure 19 Radiological anatomy of head and neck – CT image

Ultrasound

It is widely available, portable and relatively cheap. Though it has limited application in diagnosis it is useful in identifying cervical nodal metastasis and vascular invasion.

Its major disadvantage is the operator dependency and its limited application due to limited transmission through bone and air.

Computed Tomography

It is widely available, used extensively and has become the main stay for imaging and staging of primary disease. It is quick and easy to perform, produces reproducible results and provides a wide range of information. It is excellent for bony detail like mandibular erosion or skull base involvement. It allows high resolution multiplanar reconstructions which provides more information than conventional imaging modalities.

Its disadvantage is the use of radiation and its exposure, poorer soft tissue contrast and information compared to MRI, need for IV contrast for improved resolution and side effects associated with contrast, artefacts in the presence of metal objects like dental amalgam if present.

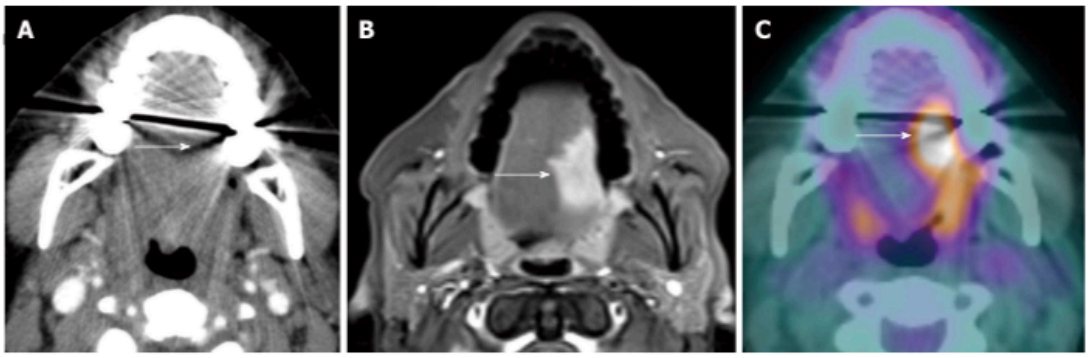

Figure 1 Dental amalgam artifact obscuring an oral cavity tumor. A: The T2 left lateral oral tongue squamous cell carcinoma (arrow) was obscured by the dental amalgam artifact on contrast-enhanced computed tomography (CT); B: The lesion is better evaluated on the contrast-enhanced T1W; C: Positron emission tomography/CT (PET/CT) images. Information from the PET portion is clearly less affected by streak artifact. However, PET/CT does not add additional information to magnetic resonance imaging in terms of primary oral cavity lesion extent for the majority of cases.

Figure 20 CT, MRI and PET CT for imaging a carcinoma of oral cavity obscured by dental artifact

Magnetic resonance imaging

It uses the principle of proton density identified by magnet to reflect biochemical tissue characteristics and identification of tissue structures. The advantage of MRI scan is the soft tissue contrast, evaluation of blood vessels without using contrast, multiplanar scanning and no radiation exposure. It can also be used to perform functional imaging like diffusion weighted imaging, perfusion and dynamic enhancement studies with the development of various magnetic gradients.

The disadvantage of MRI is the higher cost, limited availability, longer acquisition times and lack of compatibility with metal implants. In head and neck imaging, movement and swallowing artefacts and air pockets can cause distortions and degrade image quality. It requires complex algorithms for reconstruction, production of multiple sequences and requires expertise for interpretation.

Positron emission tomography – computed tomography with fluorine 18 deoxy D glucose

PET CT makes use of the metabolic nature of tumor to identify the tumor and its extension. The radiolabeled tracer is preferentially transported to the tumor by normal circulation which is detected by a gamma camera array. It is coupled with a CT for better resolution and anatomic visualization. The advantage of PET CT is the evaluation of whole body to identify the tumor in addition to lymph nodal and metastatic disease and exclusion of same.

The main drawback is the non-specific nature as uptake is increased in cases of inflammation also. It is also more expensive, time consuming, requires fasting with normal glycemic levels. It can also have false positive results due to areas of high

physiologic uptake in the head and neck region like tonsil, tongue and vocal cords.(21)

For accurate and precise management of head and neck malignancy, imaging is essential. Oral, oropharyngeal, laryngeal and hypopharyngeal lesions are initially imaged with a CT scan as it helps to acquire images fast and reduces artefacts. For better soft tissue delineated and identification of muscle invasion, MRI is useful in cases of tongue cancer. It is also useful to identify pre-vertebral muscle involvement in hypopharyngeal tumors to decide on operability. In early glottic lesions to identify minute para-glottic extension (where higher soft tissue resolution is required) MRI can be useful. For sinonasal, nasopharyngeal and salivary gland tumors MRI is more useful than CT to better identify tumor extent. PET CT is very useful in all these cases to identify extent of disease and identify occult metastasis. It is also recommended in cases of unknown primary with cervical nodal metastasis. PET CT also helps in early identification of post treatment residual and recurrent disease while on follow up. (22)

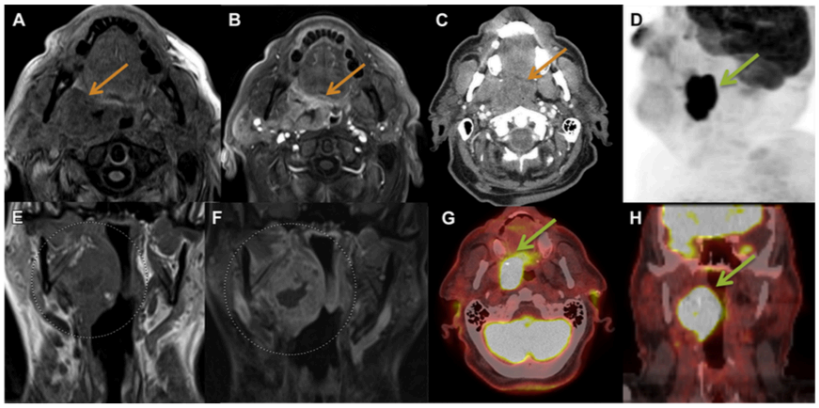

Fig. 3. Illustrating combining imaging modalities in evaluating clinical stage III-IV T3-T4 right tonsillar adenoid cystic carcinoma in 55-year-old man. Precontrast axial T1-weighted image (WI) (*A*), postcontrast axial T2WI (*B*), contrast-enhanced axial CT image (*C*), coronal PET (*D*), precontrast coronal T1WI (*E*), postcontrast coronal T1WI (*F*), as well as (*G*) axial and (*H*) coronal fused PET/CT demonstrates abnormal enhancing mass (*green arrow*) in the right tonsil, which causes mass effect and narrowing of the oropharynx with invasion of the adjacent tissues at the skull base. Radiographically, this is stage IV T4. The yellow *arrow* refers to the abnormal mass which represents the lesion on the axial CT imaging. The circles in (*E*) and (*F*) also show the abnormal mass which also represents the lesion on the coronal CT imaging.

Figure 21 Combined imaging in evaluation of a patient with right tonsil adenoid cystic carcinoma

MANAGEMENT

Management of locally advanced squamous cell carcinoma of the head and neck region consists of radiation therapy with concurrent chemotherapy. (23) Initial treatment used to be radical radiotherapy without the use of chemotherapy. Southwest Oncology group (SWOG) in co-operation with RTOG and ECOG undertook an intergroup phase III randomized trial in the late 1990s by Al-Sarraf who compared chemoradiotherapy and radiotherapy in advanced nasopharyngeal cancer. The trial was able to prove without the doubt the benefit with addition of chemotherapy to radiation therapy in the form of better 3 year PFS, median survival and overall survival. (24) MACHNC meta-analysis in 2009 (25) and its update in 2011 demonstrated an absolute improvement of 4.5% in 5-year overall survival for patients who received chemotherapy. Among these patients a 6.5% benefit was observed for patients who received concurrent platinum based chemotherapy. (26) Among all subsites, maximum benefit was observed in oropharynx and laryngeal cancers.

Radiation therapy techniques have evolved from the Telecobalt era to present state of high precision radiotherapy. With the advent of treatment planning systems and multi-leaf collimators in 1990s conformal radiotherapy became a viable option. This has resulted in highly targeted and conformal dose distribution inside target volume and at the same time sparing normal tissue in the adjacent area. This has in turn contributed to achieving better local control with lesser treatment related morbidity. The inverse treatment planning system introduced with intensity modulated radiation therapy

(IMRT) has further improved dose delivery and also treatment outcome. (27) There are various studies that have convincingly demonstrated the benefit of improved dose volume parameters for critical structures, xerostomia scores and quality of life scores for patients treated with IMRT in comparison with conventional (2D) or conformal (3D) treatment. (28–30)

The use of IMRT has also allowed dose escalation to tumor volumes and also relative acceleration of dose delivery in addition to the initial goal of sparing normal tissues. SEER database analysis has revealed that use of IMRT has resulted in cause specific survival compared to non IMRT techniques. (31) The studies which looked at cost effectiveness of IMRT used a Markov model to look at the incremental cost per quality of life year (QALY) gained by making use of IMRT. It demonstrated substantial cost effectiveness with lesser xerostomia and similar local control. (32)

There have been various studies that looked at the advantage and disadvantage of step and shoot IMRT in comparison with volumetric modulated arc therapy (VMAT). A multi-institutional study compared the quality of VMAT plans with IMRT. It was observed that the double arc plans were superior to step and shoot technique. It was also observed that the dose to organs at risk were significantly better and the treatment time was decreased by at least 50% with the use of VMAT. (33) Another NTCP/ TCP analysis comparing IMRT and VMAT plans revealed that both techniques had similar TCP. In addition, the arc plan had significantly lower maximum dose delivered to

spinal cord and also a significant reduction in MU. Both techniques had similar PTV coverage with no significant differences in homogeneity and conformity index. (34)

The ideal concurrent chemotherapy regime has been debated since the time MACH NC meta-analysis reported the benefit of chemotherapy. This difficulty in choosing the optimal regime has been mostly due to the different ways of combining chemotherapy and the heterogeneity of various study designs.(35) It has been observed the ultimate limiting factor in intensifying treatment is patient related, disease specific and related to the environment and the intensification most likely results in high acute morbidity requiring intensive support. The three weekly chemotherapy regimen with 100 mg/m2 cisplatin delivered concurrently with radiation has been established in the historic trials as the standard of care. (36–38) A more recent randomized control trial from Tata Memorial Hospital was able to demonstrate the superiority of 3 weekly cisplatin over weekly cisplatin schedule. (39) However the toxicity of this has resulted in more than 60% patients not receiving the full recommended chemotherapy which eventually translates to poor outcome in view of sub optimal treatment. (40) This is more challenging in a resource limited country like India. An alternate regimen with weekly low dose cisplatin has been used commonly which has resulted in lesser requirement for supportive care, increased dose intensity, lesser toxicity and also better radio-sensitization and decreased risk of resistance. (41)

The role of epidermal growth factor receptor (EGFR) has been extensively researched once it's over expression has been brought to the attention of researchers world over.(42) It's over expression has been consistently associated with poorer response to radiation therapy and resistance and an overall poorer prognosis. (43) A molecule of particular interest was a monoclonal antibody with anti EGFR effect called Cetuximab. Its use concurrently with radiation therapy was studied in a phase III randomized control trial for locally advanced head and neck cancer. It was observed that its use resulted in significantly better 5 year overall survival compared to radiotherapy alone. (44) These results lead to an early adoption of the drug in clinical practice in spite of increased toxicity. (45) The search for a less toxic alternate drug has resulted in the development of a humanized form of the drug called Nimotuzumab. It binds to the extracellular domain of EGFR receptor and inhibits receptor – ligand binding. This has been associated with far less incidence of adverse events. A phase II study had reported that the drug was safe and well tolerated for concurrent administration with radiation and provided long term survival benefit. (46) Most recent data have looked into the role of immunotherapeutic agents like Nivolumab and Pembrolizumab in head and neck squamous cell carcinomas.

ROLE OF PET CT IN HEAD AND NECK CANCERS

^{18} FDG PET CT is being increasing utilized in the management of head and neck malignancies. Its applications include diagnosis by directing biopsy, staging, detecting primary in occult nodal metastasis, defining tumor volumes, treatment response assessment and in detecting local and distant metastasis post treatment while on follow up. The most important and indispensable role has been in detecting an unknown primary and early detection of recurrence or a residual disease. (47)

Diagnosis of an unknown Primary Tumor

The clinical presentation of 5-10 % patients is cervical lymphadenopathy without an obvious primary tumor detected on clinical examination and routine imaging. Studies by Rusthoven et al and Zhu et al have demonstrated added detection rate with ^{18} FDG PET CT with high sensitivity and moderate specificity compared to conventional imaging modalities. Benefits of detection of a possible primary tumor site include option of targeted biopsy, surgical excision of identified primary and also reduction in volume of radiation target volume. (48)

Staging

Initial staging of the disease is very important to plan treatment and determine prognosis. ^{18} FDG PET CT can provide accurate information regarding primary tumor, nodal and distant metastasis and presence or absence of a second primary carcinoma.

Staging of Primary Tumor (T)

For evaluation of primary tumor, ^{18} FDG PET CT is more effective than CT or MRI. It can provide more information and has higher sensitivity compared to CT or MRI. The metabolic information obtained from PET scan supplements the anatomic information from CT scan. To identify mandibular invasion, PET CT had better sensitivity and specificity than CT scan alone. (49) Another advantage of PET CT is in the identification of synchronous primary malignancies which can arise due to field cancerization seen commonly in head and neck malignancies. False negative results can occur when small or superficial tumors are being evaluated and false positive results occur when the location of tumor is in areas of high physiological uptake. For example, in an oral cavity primary, if the location of the tumor is close to dental amalgam filling the presence of artifacts can make it difficult to identify the tumor and delineate it accurately. Limited spatial resolution of ^{18} FDG PET restricts the ability to accurately delineate the tumor and its relationship with surrounding structures but, on combining with an anatomic imaging modality like CT or MRI improves this pitfall. Hence it is always advised to combine ^{18} FDG PET with contrast enhanced CT or MRI for accurate information.

Staging of Nodal Disease (N)

Nodal metastasis can significantly affect staging, treatment plan, prognosis and overall survival. It is the most important factor affecting prognosis in head and neck squamous cell carcinoma. ^{18} FDG PET CT has superior sensitivity and specificity compared to CT or MRI in detecting occult nodal metastasis. (50) In patients with

clinically node negative neck it was found that ^{18} FDG PET CT was superior to CT and MR imaging in detecting occult metastasis. Its use decreased probability of occult nodal metastasis by up to 12% compared to clinical examination, CT or MRI alone. (51) The significant advantage that ^{18} FDG PET CT has over conventional imaging modalities is that it can detect morphologically normal but metabolically active lymphadenopathy. These would have been identified as normal if either CT scan or MRI was used for staging purpose. In primary lesions of oral cavity, oropharynx and supraglottic larynx with clinically N0 neck, risk of occult nodal metastasis is about 20-30%.(52) The decision to electively radiate the neck or undergo neck dissection depends on this and the utility of ^{18} FDG PET CT to identify this early improves the prognosis for the patient.(48)

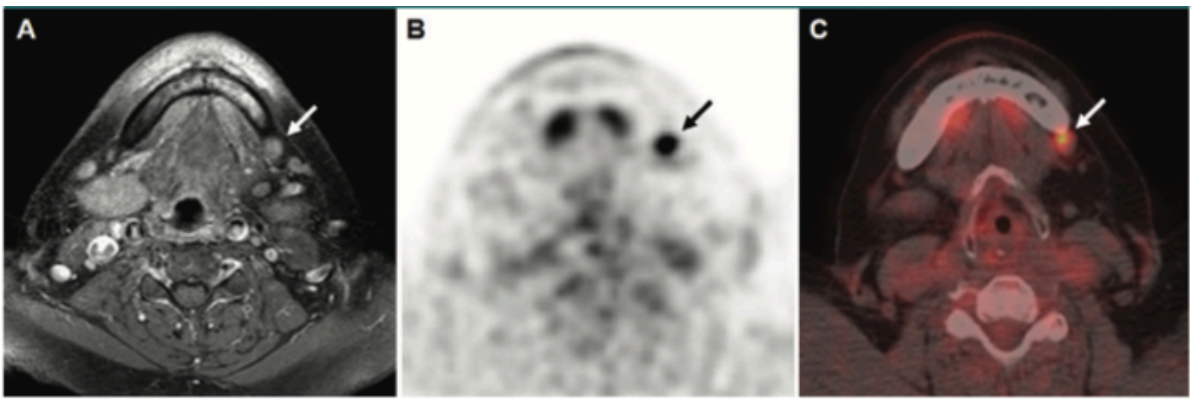

Figure 1: Images show preoperative detection of metastatic lymph nodes in a 66-year-old woman with oral cavity cancer and negative neck palpation findings. *A*, T1-weighted gadolinium-enhanced MR image shows an oval lymph node (arrow) in the left cervical level II; its size suggests falsely that it is a benign node. *B*, ^{18}F-FDG PET and *C*, fused PET/CT images show a true-positive finding with strong ^{18}F-FDG uptake (arrows).

Figure 22 Preoperative detection of occult lymph node by PET CT

Metastasis (M)

^{18} FDG PET CT is also useful in detecting distant metastasis. Though the incidence of distant metastasis in head and neck squamous cell carcinoma is low compared to other primaries the incidence of the same increases with locally advanced disease (T3-T4) or (N2-N3), perineural invasion and extracapsular extension in the involved lymph nodes and would influence the treatment modality. The national comprehensive cancer network (NCCN) recommends that ^{18} FDG PET CT be done for primary evaluation of advanced stage (III and IV) primaries of oral cavity, nasopharynx, oropharynx, larynx, mucosal melanoma and unknown primary. It is because distant metastasis was commonly seen when etiological causes like alcohol or tobacco use was implicated. ^{18} FDG PET CT detected these distant metastases with much better accuracy as compared to conventional imaging modalities. (50) PET CT biomarkers identified in the pre-therapy or diagnostic scan like maximum SUV (SUV_{max}), metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been reported to be associated with worse patient outcomes.(53–55)

Radiotherapy planning and tumor volume delineation

Radiation therapy had made tremendous progress from previous conventional open field RT to precision radiotherapy using techniques like IMRT. This progress demands accurate tumor identification which in turn helps to identify target volumes and organs at risk better. These advancements have led to achievement of better therapeutic ratio by improvement in tumor coverage with the potential for dose escalation while sparing the surrounding organs at risk. Improvements in the field of diagnostic radiology has enabled this to a great extent. ^{18} FDG PET-CT which

acquires co-registered PET and CT images allows the acquisition of the whole body anatomic and functional images during the same procedure. (56) ^{18} FDG PET CT derived Gross Tumor Volume (GTV) is usually smaller than conventional GTV and is more accurate. When a comparison was made between GTVs obtained from PET-CT, CT and MRI, PET-CT had 97% accuracy compared to 69% for CT only and 40% for MRI alone. In another study when volumes were compared, the GTV obtained from CT alone differed significantly from the GTV obtained from PET-CT in 56% of patients and in 46%, there was a 20% change in PTV. It was observed that inter-observer variability was also significantly less when PET-CT was used. (57) Different methods could be used to delineate the PET-CT tumor volume like Source to background ratio (SBR) segmentation, border criterion of 50% of the maximum standardized uptake value (SUV50), visual interpretation and auto-segmentation.

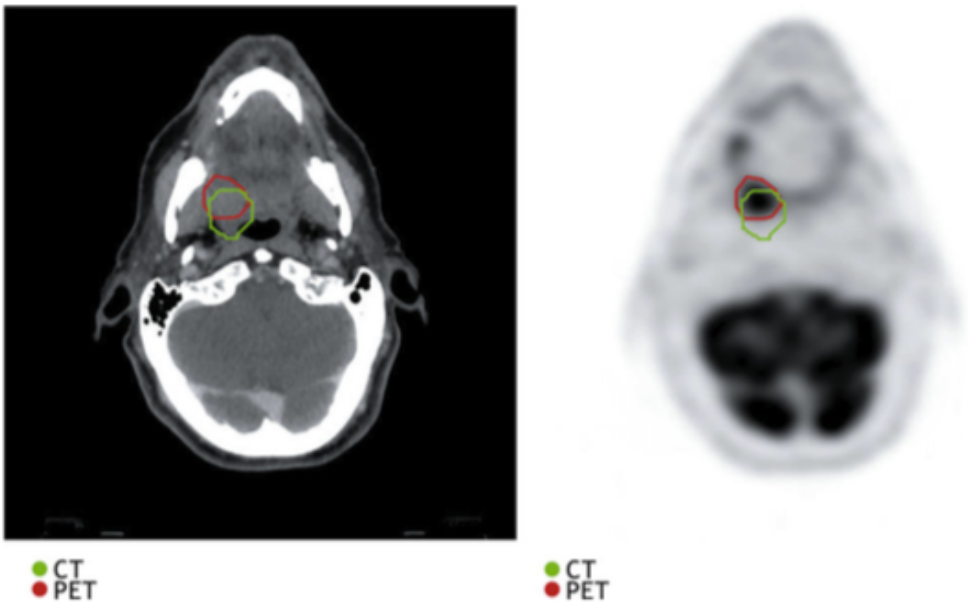

Figure 23 Discordant CT and PET-CT GTV

In general, the tumor volume delineated by using PET-CT information was much smaller than the CT volume but this varies greatly with the segmentation or delineation strategy used. Therefore it could also be the same size or even bigger than GTV identified on CT with significant non-overlap of the GTV PET volume with GTV CT volume and this was attributed to be due to presence of peri-tumoral inflammation. ref To mitigate this difference some authors had also proposed a background-subtracted relative threshold level method which obtained reliable thresholds independent of the signal-background ratios.

Some authors had compared the PET volumes with pathological specimen using frozen specimens and volumetric assumption strategy. This method also failed to identify the most appropriate method to delineate the tumor volume accurately but was able to adequately prove that ^{18} FDG PET was the most accurate modality when compared to CT and MRI. (58) In spite of all hypothesis the current segmentation techniques does not approximate tumor volume accurately and what has been suggested is an integration of both signal to background ratio and threshold SUV based strategy. (59)

PET Signal changes during therapy

Historical data has identified that anatomic changes that occur during the standard course of radiotherapy that extends for 5-7 weeks. PET-CT done during the course of radiotherapy has demonstrated that beyond fourth week of radiation the reliability of PET CT to identify tumor cells decreased. This was because the number of viable tumor cells decreased drastically whereas the inflammation in the surrounding tissues

showed an increasing trend with the increase in glucose avid macrophages in the surrounding regions showing a high SUV uptake.

Dose escalation

Dose escalation in radiation therapy of the head and neck regions have been shown to provide better local control which may in turn improve the outcomes of treatment. The main problems which arise when we consider dose escalation is the higher dose of radiation that the normal surrounding tissue receives. [18] FDG PET provides biologic information regarding the tumor in addition to the anatomic data which promotes accurate delineation and identification of the tumor separating it from the surrounding normal tissue. Integration of [18] FDG PET CT in IMRT planning is beneficial by treatment individualization and dose escalation. The volume delineated obtained by integrating [18] FDG PET CT is usually smaller and it leads to better dose distribution and escalation in dose to tumor alone and this in turn helps to better spare OARs like parotid gland. Due to this dose escalation with significant reduction in toxicity was possible and was carried out by a method called dose painting. Dose painting was defined as locally boosting the tumor to increase locoregional control based on functional imaging. It facilitates mapping of dose prescription to non-uniform distribution of biochemical, metabolic and molecular abnormalities within the tumor. When a higher BED of 92.9-95.8 Gy was delivered to tumor by dose painting, it was associated with better complete response rates and lower risk of local residual disease associated with better LFFS, DMFS and OS compared to the group that received a BED of 85.9-88.6 Gy. Though the dose escalated group did report increased acute toxicities during the course of treatment they tolerated the higher dose delivered well

since the volume to which escalated dose was delivered was small. Late toxicities were found to be similar between the groups.(60)

Response assessment

Concurrent chemotherapy has been considered as standard of care for treatment of head and neck squamous cell carcinoma since it can provide better locoregional control and survival when compared to radiotherapy alone. Even with improved results compared to radical radiotherapy alone about 20-30% and 10-15% develop recurrences in the primary site or neck respectively within first 2 years of follow up. The estimated median survival if a patient develops recurrence is dismal with a survival less than 1 year if left untreated. Hence it becomes paramount to assess response to treatment and detect recurrences early to administer appropriate treatment, either salvage surgery or best supportive care. The need for a post treatment evaluation tool that reliably predicts patient's clinical evolution in the first years of follow up was therefore important and in view of its higher sensitivity and specificity there probably is no technique better suitable for this than ^{18} FDG PET CT. (61,62)

Conventional imaging modalities utilize size and other anatomic parameters to assess response to treatment. In view of this, non-surgical treatments can cause significant distortion to tumor shape and size and other anatomic parameters due to edema, fibrosis and vascular changes, it cannot measure the viability of the tumor which should be the ideal parameter to assess response. It is here that ^{18} FDG PET CT that scores over conventional modalities as the changes in glucose metabolism closely co-relates to the viability of the cell. A study by the French group demonstrated that

when a response assessment PET CT was done 12 weeks after treatment completion and the results were compared to histology in case of residual disease, the sensitivity, specificity, positive predictive value and negative predictive value were 86.7%, 90%, 76.5% and 93.1% at the primary site and 100%, 97.2%, 87.5% and 100% in the neck. They concluded that ^{18} FDG PET CT was effective in detecting residual disease and in predicting recurrent disease within the first 2 years of follow up after non-surgical treatment(61)

Table 1 Hopkins criteria for PET CT response assessment

Score	^{18}F-FDG Uptake Pattern	Response Category
1	^{18}F-FDG uptake at the primary site and nodes less than IJV.	Complete metabolic response
2	Focal ^{18}F-FDG uptake at the primary site and nodes greater than IJV but less than liver.	Likely complete metabolic response
3	Diffuse ^{18}F-FDG uptake at the primary site or nodes is greater than IJV or liver.	Likely postradiation inflammation
4	Focal ^{18}F-FDG uptake at the primary site or nodes greater than liver.	Likely residual tumor
5	Focal and intense ^{18}F-FDG uptake at the primary site or nodes.	Residual tumor

Note—Scores 1, 2, and 3, which represent complete metabolic response, likely complete metabolic response, and likely postradiation inflammation, respectively, are considered negative for tumor. Scores 4 and 5, which represent likely residual tumor and residual tumor, respectively, are considered positive for tumor. New lesion would be considered as progressive disease. IJV = internal jugular vein. (Reprinted with permission from [61]: This research was originally published in *JNM*. Marcus C, Ciarallo A, Tahari AK, et al. Head and neck PET/CT: therapy response interpretation criteria (Hopkins criteria)—interreader reliability, accuracy, and survival outcomes. *J Nucl Med* 2014; 55:1411–1416 © by the Society of Nuclear Medicine and Molecular Imaging, Inc.)

Hopkins criteria shown above was one of the earliest criteria used for response assessment before biomarkers were incorporated (63)

PET CT Biomarkers

Standardized Uptake Value

Standardized Uptake Value (SUV) is a semi-quantitative measure of the normalized concentration of radioactivity in a tumor or lesion of interest. The radiotracer FDG is the most commonly used clinically and it represents the glucose metabolism in the cell

and the value can be used as a surrogate marker for the metabolism in the tumor. An association can also be made between the SUV value and tumor burden or stage. Aggressive tumors in general have high tumor burden and as a result high metabolism correlated by higher SUV value. This has correlated with treatment outcome even for different tumors of the same stage and size. Thus, in addition to tumor stage or burden it also expresses some intrinsic biological characteristic of the tumor.(64)

SUV measurement can be done in a 2D region of interest (ROI) or 3D volume of interest (VOI). The radioactivity measured at the ROI of interest has to be normalized to the average radioactivity concentration in the patient's body. The average radioactivity concentration is approximated as the injected dose divided by the patient's body size, weight or body surface area. SUV is the ratio of tissue radioactivity concentration and injected activity divided by the weight of the patient. The value was influenced by various factors such as tissue activity, tissue state, time from injection to imaging and normalization factors. Instead of body weight, some authors also use lean body weight or body surface area.

SUV_{max}

The highest voxel value within a VOI or ROI is referred to as SUV_{max}. SUV_{max} is the most commonly used parameter to measure metabolic tumor activity in oncological imaging. It is usually measured by surrounding the target lesion with a 3D VOI or drawing multiple 2D ROIs in different axial slices and interpolating it to detect the highest activity. The advantage of SUV_{max} over SUV_{mean} is that it is more reproducible and less observer dependent. SUV_{max} also has application in various stages of

management for example, at baseline, during treatment, early and late post treatment and during follow up of patients.

Baseline SUV_{max}

Factors that showed correlation with the baseline SUV_{max} value were T, N stage, local control and DFS; higher value leading to poorer outcome. It was also found that higher baseline SUV_{max} was associated with poor tumor differentiation, extracapsular spread, skin invasion and absence of perineural invasion. (54)(64)

Multiple studies have shown that baseline SUV_{max} has been consistently associated with advanced stage, large tumor size poor differentiation and outcome but the association between baseline SUV_{max} and tumor recurrence has not been well established. In a retrospective study that analyzed baseline SUVmax with respect to survival in head and neck squamous cell carcinoma treated with radiotherapy with or without chemotherapy, Machtay et al found that 2 year DFS rates varied between 76% for patients with SUV_{max} <9.0 and 37% for patients with SUV_{max} >/= 9.0 (p=0.007). The difference in outcome between the groups were as significant as the difference seen with respect to tumor, node and metastasis stage. This suggested that SUV_{max} can be used as a valuable biomarker that can help predict response and survival and thus guide the aggressiveness of therapy. (53)

The cut-off for significant SUV_{max} value for high and low varied between studies mostly due to the heterogeneous patient population and the intrinsic variability in PET CT Scanners. It has been observed in general that an SUV_{max} > 9 has been consistently associated with worse overall and progression free survival regardless of the treatment. It has also been hypothesized that patients with SUV_{max} >9 should receive

more aggressive treatment and the ones with less < 9 should receive less aggressive treatment. (53) But this is yet to be validated in large prospective trials.

SUV_{max} and therapy response

Post treatment ^{18} FDG PET CT is useful to decide subsequent management as it can predict pathological response and long-term survival. Change in SUV as a surrogate to response assessment was studied by Lowe et al. He prospectively studied mean SUV change between pre-therapy and post-therapy PET scan and it was 34% in patients with residual disease and 82% in patients having pathologically complete response. (65) Prospective data using PET CT for evaluation revealed a significant difference between DFS and OS between complete metabolic responders and non-responders. Analysis of predictive value of post treatment SUV_{max} done, revealed that patients with low primary tumor SUVmax in the post treatment period had a reduced risk of progression and death by 83% and 72% respectively. It was also observed that change in the SUV_{max} of primary tumor was a better parameter than change in nodal SUV_{max} in assessing response to treatment. Though the absolute degree of change in SUVmax has not been ratified, it has been well proven that change in SUV_{max} is a better predictor of response and outcome when compared with other biomarker parameters. Patients with change in SUV_{max} of 60-100% and post treatment SUV_{max} < 3 have been found to have better overall and disease free survival and local control at 2 years. (66) The role of PERCIST criteria will be detailed in the later section.

SUV_{max} and follow up

The role of ^{18} FDG PET CT in follow up is high due to its ability to detect local recurrence, regional lymphatic spread and distant metastasis. The accuracy for same varies based on the time interval between treatment completion and imaging. It is generally recommended to do response assessment scan beyond 12 weeks rather than immediately after treatment completion. A meta-analysis compared diagnostic accuracy of scans done less than 12 weeks after treatment and more than 12 weeks after treatment. For the evaluation of primary tumor, there was no significant difference was seen (p=0.1266), but for the evaluation of nodal disease, scans obtained after 12 weeks showed better accuracy. The sensitivity and specificity in scans prior to 12 weeks was 62.5% and 85.1% respectively. But it increased to 90.4% and 94.3% when the imaging was done after 12 weeks post treatment. (p=0.0003) (67)

SUV_{mean}

SUV_{mean} was a concept developed to negate the effects of SUV_{max}. It uses information from multiple voxels thereby making it less sensitive to image noise. But this makes it subject to both intra and inter observer variability since it depends on the voxels which were chosen to calculate the average and ROI. Due to this it is not as commonly used as a metabolic biomarker as SUV_{max} and there are limited data only available to support its use. Studies have shown that high SUV_{mean} at baseline and change in SUV_{mean} post treatment correlates well with survival and locoregional control.

SUV_{peak}

SUV_{peak} is a hybrid SUV measurement that includes a local average SUV value in a group of voxels surrounding the voxel with highest demonstrated activity. This concept was developed to maintain the high reproducibility of SUV_{max} while reducing noise with improved statistics. In clinical imaging with noise properties typically associated with whole body studies SUV_{peak} was shown to be a more robust alternative to SUV_{max} to assess the most metabolically active tumor region. It has not yet been used in a standardized way and has not been used for routine reporting yet.

Metabolic Tumor Volume

Metabolic tumor volume (MTV) is defined as the volume of tumor that demonstrates FDG uptake. It is a combined metabolic and volumetric biomarker that can estimate the volume of tumor based on the distribution of metabolic activity. The usual biomarkers like SUV_{max} is a single pixel representation of maximum FDG uptake whereas MTV can quantify the overall tumor burden. Volume based parameters were sought to identify methods that can more accurately identify true tumor burden, better predict outcome and hence prognosticate disease. There are different methods mentioned to accurately and appropriately segment MTV. The most commonly used methods include an absolute or fixed percentage SUV_{max} threshold and gradient or adoptive segmentation methods. (66)

Various studies have demonstrated that baseline MTV correlated with short term outcome including residual disease and recurrence, local control rates and even overall survival. It has also been noted that tumor MTV was a significant predicting factor than nodal MTV. It has also been demonstrated in these studies that baseline

metabolic tumor volume was the biomarker that correlated with these factors and not baseline SUV_{max}. Though a specific MTV value has not been identified with patients likely to have poorer outcome it was observed that higher value consistently had worse outcome.

Change in MTV post treatment has also been studied and it has been shown that an increase in value was associated with poorer outcome demonstrated by disease progression and decreased survival. It represented a more accurate predictor of overall tumor burden than single pixel SUV_{max} values.(66)

Total Lesion Glycolysis (TLG)

It is defined as metabolic tumor volume multiplied by SUV_{mean} of included voxels). It factors in both metabolic tumor and SUV; that is, it represents both degree of FDG uptake and size of tumor. It theoretically represents the total activity of metabolically active tumor cells within the volume of interest. Studies have demonstrated that a high TLG value was associated with poorer overall survival, disease free survival and local failure free survival rates. In a study by Moon et al, 69 patients with squamous cell carcinoma of oropharynx was evaluated and it was found that TLG was the only significant prognostic factor that was associated with a decrease in overall survival when compared with SUV and MTV. It is also a better predictive value than MTV in determining time to event. (55)

FDG biomarkers like TLG and MTV that factor in volumetric information seems to be more valuable in predicting outcome for patients with head and neck squamous cell carcinomas but it is yet to be established in large prospective studies. Moreover, its repeatability and reliability is yet to be established before it can be incorporated into

routine clinical practice. Earlier these were not commonly used in routine clinical practice due to need for complex manual calculations and lack of availability of software programs to calculate it. But now most clinical software used in nuclear medicine and radiation oncology has provision to calculate it at the click of a button. Once it becomes more accessible and mainstream it could be incorporated into more prospective trials and the data obtained should help us incorporate this data in decision making in our routine clinical practice.

PERCIST Criteria

With the advent of ^{18} FDG PET CT and its common use in diagnosis, staging, planning and response assessment a need for a guideline to systematically assess response to treatment in patients with cancer in a structured manner arose. The guideline had to be suitable for clinical use for routine PET reporting and also potentially in trials. Professor Richard Wahl first put forth the concept of PERCIST 1.0 in 2009 and it described in detail the methods for controlling the quality of ^{18} FDG PET imaging conditions to make sure that the PET images from various time points were comparable and also to ensure that quantitative expression of changes in PET measurements and the assessment of PET results for overall response was feasible. Since its publication it has been widely adopted, referenced frequently and published data has revealed that the metrics of PERCIST 1.0 were associated with clinical outcomes after treatment in patients with a wide variety of malignancies like colorectal cancer, small cell lung cancer, Ewing sarcoma, non-Hodgkin lymphoma and esophageal cancer. Though the most commonly used method historically for assessment was visual assessment, it had high inter observer variation and only a simple categorization of patients into 2 groups as responders or non-responders. Therefore, this was grossly inadequate and it failed to capitalize on the rich quantitative data that PET can provide. When it is presented as percent change in FDG uptake it retains the inherently continuous nature of data and it also has high inter observer reproducibility. (68)

Parameters required for Baseline ^{18} FDG PET study

Baseline requirement is the measurement of the single tumor that appears as the hottest along with background area on images, commonly of the liver. This measured background info is used to ensure that the study was performed properly technically and also to ascertain a threshold value appropriate for standardized uptake value (SUV) corrected for lean body mass. The minimum threshold for measurability is defined as 1.5 x (mean value of normal liver) + 2 x (standard deviation of liver)

Lean body mass can be calculated for men and women by the following formula.

$$\mathrm{LBM}_{\mathrm{James}} = \begin{cases} 1.1 \times \mathrm{BW} - 128 \times \left(\frac{\mathrm{BW}}{\mathrm{Height}}\right)^2 & \text{Men} \\ 1.07 \times \mathrm{BW} - 148 \times \left(\frac{\mathrm{BW}}{\mathrm{Height}}\right)^2 & \text{Women} \end{cases}$$

Figure 24 James's equation for calculation of lean body mass

James's equation for calculation of Lean body mass (69)

PERCIST criteria uses a single target lesion at each time point as the primary parameter. This is based on the concept that the area of the tumor which is most metabolically active usually corresponds to the most aggressive portion of the tumor and that by default makes it the most important area clinically. This is similar in principal to the RECIST criteria which is detailed in another section. Even though in clinical practice SUV_{max} is used, with PERCIST a larger area of interest, the peak standardized uptake value corrected for lean body mass (SULpeak) is used since the size of a single voxel can vary widely between the various PET systems and this can

result in considerably high noise levels depending on the filtering. SUV_{max} is also associated with upward bias in studies that use low count when compared with SUV_{peak}.

Background activity

To calculate the background activity, a 3-cm diameter volume of interest, spherical in shape is placed on the right side of the liver (hepatic SUL), which is midway between the inferior margin and dome while the central ducts and vessels are excluded. The reason for choosing liver is that the FDG does not accumulate greatly in white fat when the study is performed in fasting state. Also, the hepatic SUL is typically more consistent between patients when compared with total body mass standardized uptake value. The SUL and standard deviation of the measured SUL within the spherical VOI are measured to 2 significant digits. There are 2 typical scenarios that may arise when calculating the background activity. Firstly, if the liver is diseased, the mean background SUL and its standard deviation can be measured in a cylindrical VOI whose diameter is 1 cm and has a 2-cm long axis parallel to descending aorta in the center of descending aorta while excluding the wall of aorta. Secondly, if the patient has metastasis in the liver, 3 cm diameter VOI has to be drawn without including obvious metastatic tumor. Current computer systems have the capability to measure mean of a chosen VOI by calculating the average of all pixels that form a part of the VOI.

Baseline target lesion

As mentioned before SULpeak has to be measured in the single hottest tumor. A 1-mL spherical VOI has to be placed at the area of focus in the hottest tumor. This can be

done either manually or automatically with the use of computer software. A routine visual inspection is usually sufficient to identify this area of increased uptake that are consistent with tracer uptake in malignant lesions. It is important to exclude structures like renal pelvis. The SULpeak 1 mL VOI is centered on the voxel with highest maximum SUL and in some cases, it may be observed that it may not include the pixel with maximum SUL.

Mathematically, a 1.2 cm diameter spherical VOI provides a volume of approximately 1 mL. The practicality of this depends on the image voxel size and implementation details of the VOI computing software. The VOI volume can also depend on its position, because the same VOI can produce slightly different volume measurements depending on how exactly it is positioned in relation to the centers of voxels.

For measurability criteria for a tumor is that its SULpeak has to be greater than or at least equal to one and a half times the mean SUL in the 3-cm diameter spherical VOI plus two times its standard deviation to have a minimum threshold for evaluation. Also, a minimal level of tumor uptake at baseline proposed to ensure that a decline in FDG uptake with the treatment administered can be measured within the dynamic range of the imager to decrease the probability that a change is due to chance and also to minimize overestimation of response or progression. To ensure this if the SULpeak of a tumor at baseline is below this threshold the tumor cannot be measured by PERCIST 1.0. This is applicable only at the baseline study. If a target lesion is immeasurable at the baseline scan, then it should be noted that the measurement of the lesion is below the minimum required threshold for evaluation. The minimum threshold which should be used as optimum for reliable evaluation of a lesion is not

known. This concept is proposed due to the reason that the lesions which show low FDG uptake has limited ability to show a decrease in SUL of 30% required for PERCIST criteria and background activity may contribute substantially to the residual signal intensity. It should also be noted that if a new lesion develops on follow up or there is unequivocal progression, it does not matter even if the target lesion at baseline did not meet the minimum threshold for evaluation. Hence the concept of minimum threshold is applicable only for baseline evaluation.

Assessable ^{18} FDG PET CT and Measurable Target Lesion

To minimize variability and to ensure correct performance of PET it is recommended that the image acquisition methods are followed that are recommended by National cancer center. For a lesion to be assessed by PERCIST, the mean SUL and imaging conditions of liver have to be stable, the differences between baseline and follow up SUL in the liver must be (a) less than or equal to 20% of the larger of the two liver measurements and (b) less than or equal to 0.3 SUL units. For this to be made possible the imaging conditions should be such that (a) the variation in time between injection to imaging for both the studies should be less than or equal to 15 minutes. (b) The time of injection to the time of initiation of imaging should be either greater than or equal to 50 minutes and less than or equal to 70 minutes (Minimum uptake time of 55 minutes). (c) The imaging equipment used must be same and same area has to be imaged. (d) The same protocol for image acquisition, reconstruction and same version of software has to be used. (e) The difference between the doses of FDG injected between both the studies have to be less than or equal to 20% in megabecquerel units.

(f) The has to be fasting for a minimum of 4 hours and the serum glucose levels before the imaging has to be less than 200 mg/dL.

Target lesion is the assessable lesion with maximum SUV uptake and non-target lesion is any other measurable lesion with SUV uptake less than the target lesion.

Objective Response

The percentage change in the metabolism of the tumor has to be recorded as a continuous variable with notation of the number of weeks since treatment began. It is calculated as

100 x [FTL SULpeak - BTL SULpeak]/ BTL SULpeak

FTL SULpeak – SULpeak of follow up target lesion

BTL SULpeak – SULpeak of the baseline target lesion

Since this method is cumbersome and complicated for routine clinical practice, PERCIST has grouped the therapeutic response seen into 4 categories which are similar to the Response Evaluation Criteria in Solid Tumors (RECIST) and the European Organization for research and treatment of Cancer (EORTC) recommendations. The PERCIST treatment responses are grouped as complete metabolic response, partial metabolic response, stable metabolic response and progressive disease.

1. Complete metabolic response – A lesion can be categorized to have complete metabolic response when it demonstrates complete resolution of FDG uptake, with an FDG uptake less than mean SUL of liver and is indistinguishable from that of the surrounding background. It also means that no new lesion with

which demonstrates FDG avidity typical of cancer is detected. If no FDG avid lesion is demonstrable on visual inspection, the mean SULpeak of the corresponding anatomic location as close as possible to the original tumor should be measured but at the same time an area of high physiological uptake has to avoided. It does not necessitate that the SULpeak to decrease to zero for a lesion to be labelled as complete metabolic response.

2. Partial metabolic response – A lesion can be categorized to have partial metabolic response if a decrease greater than or equal to 30% and also of at least 0.8% SUL units be demonstrated between the hottest evaluable lesion at baseline and the hottest evaluable lesion at follow up. It doesn't mandate that the same lesion be measured from both the studies. It requires a decline in SULpeak of greater than or equal to 0.8 SUL units in the target lesion, no new FDG avid lesion with avidity typical of cancer, on obvious increase in size more than 30% of the target lesion and no SULpeak or obvious increase in size more than 30% in a non-target lesion.
3. Progressive metabolic disease – A lesion can be categorized as progressive metabolic disease if it shows an increase of greater than or equal to 30% and an increase of at least 0.8 SUL units in a target lesion or development of a new lesion or more than one lesion. Progressive disease can include an increase in SULpeak or an identifiable anatomic increase in size which is greater than or equal to 30% in target lesion or unequivocal progression in non-target lesions and development of new FDG avid lesion in a pattern typical of malignancy.

When documenting response, the percentage change in SULpeak and time in weeks after the treatment has begun needs to be mentioned. For the calculation of duration of overall response, date of best response is subtracted from the date when progressive or recurrent disease was first noted.

Table 2 Scenarios for Target and Non-target lesions showing different responses at follow up and overall response synthesis

Original Target response	Original Non-Target Response	Overall response
CMR	PMR	PMR
CMR	SMD	PMR OR SMD
CMR	PMD	PMD
PMR	CMR	PMR
PMR	SMD	PMR OR SMD
PMR	PMD	PMD
SMD	CMR	SMD
SMD	PMR	SMD
SMD	PMD	PMD
PMD	CMR	PMD
PMD	PMR	PMD
PMD	SMD	PMD

Special scenarios in PERCIST

1) Size measurement

   It is very uncommon for a target lesion to show increase in size while having a decline in FDG uptake. Though PERCIST does not mandate a measurement of tumor size, it could be made when a visible increase in size accompanies a decrease in FDG uptake. This most common causes for the same are a cystic tumor, delayed interval between baseline imaging and initiation of treatment, delay between baseline and post treatment imaging, intra-tumoral hemorrhage or necrosis.

2) Non-target lesions

   The presence of a non-target lesion that behaves differently from a target lesion is sometimes problematic. It is possible for a non-target to have a change more than 30% in SULpeak and still be missed because only the single hottest lesion is required for routine PERCIST assessment. Hence an increase greater than 30% in a non-target lesion is not currently called progression in PERCIST 1.0. Occasionally a lesion which was labelled as non-target can become target in the follow up study due to increase in FDG uptake making it the hottest lesion.

3) Unequivocal progression

   Though it is not mentioned in PERCIST 1.0, unequivocal progression in a non-target lesion is defined when there is progression at least as much as the target lesion, a 30% and 0.8 SUL units increase and possibly more. At present, there is no strict criteria for determination of progress in a non-target lesion.

4) New Lesion

Clinical judgement should be used to identify a new lesion and the number of lesions must also be counted. A lesion can be identified as new when it is first identified, even if in retrospective review. It is also possible that the lesion was present in the baseline imaging but it was not identified due to its small size or low FDG uptake. The timing of appearance of the new lesion is taken as the time when it is first unequivocally identified.

5) Defining peak value

The computer software used in different systems use different methods for the calculation of peak value. There is a lacuna of current evidence on the ideal method to be used for calculation of the same; either whole pixel or of sub-segmented parts of the pixel. With recent advances in image resolution and filtering it is unlikely to make a major difference in the result. In some tumors with central necrosis the positioning of the 1-mL VOI may be in the periphery of the tumor when the hottest tumor focus is in the periphery. This may lead to part of the VOI being positioned partly outside the tumor boundary that has been predetermined.

6) Number of lesions

The PERCIST criteria requires only the hottest single target lesion for assessment to keep it simple and also to reflect the characteristics of the most active tumor, the optimum number of lesions to evaluate is unclear. The rationale for measuring only the single measurement could be that it identifies

the worst behaving lesion, especially when tumor resistance to therapy begins to evolve.

It has been suggested that the volume of the target tumor, the most metabolically active tumor volume be also explored in future as part of PERCIST criteria.

The actual predictive and prognostic value of PET CT is yet to be validated in the clinical setting without any doubt. Automated and semi-automated approaches in the future are expected to help in making its calculation easier for application in clinical practice. The role of other biomarkers like metabolic tumor volume and Total lesion glycolysis are being explored at present.(70)

RECIST Criteria

In the year 2000, the RECIST criteria was published and this was put forth due to the limitations of the WHO criteria which was commonly used in practice till that point of time. The main purpose of it was for it to be used in clinical trials which were looking into tumor response assessment for it was the time when cross sectional imaging with CT and MRI had entered the practice of oncology.

RECIST was able to specify the number of target organs that had to be selected as up to 10 but it did not specify how it had to be selected except that the number of lesions per organ should not be more than 5. It also mentioned that when trans axial imaging is being done only the single longest dimension of the tumor has to be measured. It also stated that the sum of these unidimensional measurements had to be used as the metric for determining response to treatment. RECIST stated that the minimum size of a lesion to be measured was 1 cm. the lesions which were adequate in size for measurement were labelled as “measurable”. All target lesions are measurable and some non-target lesions are measurable. Both can contribute towards disease progression and also to complete response.

The RECIST categories for response are

1. Complete response – The disappearance of all tumor foci for a duration of at least 4 weeks
2. Partial response – A decrease in size of at least 30% in tumor diameters for a duration of at least 4 weeks

3. Stable disease – Neither partial response or progressive disease
4. Progressive disease – At least 20% increase in the sum of all tumor diameters from the lowest tumor size.

A 20% increase in tumor diameter leads to 44% increase in the bidirectional product which is more than the 25% in the earlier WHO progression criterion. Hence for a lesion to be recognized as progression, it needs to be much bigger than required by the WHO criterion. When progression is determined by the development of new lesions both methods are concordant.

Challenges in RECIST criteria were in certain pediatric tumors, tumors with great deal of cystic changes or central necrosis like GIST and unusually shaped tumors like mesotheliomas.

RECIST 1.1

This was published as an update to RECIST n 2009 which included various updates and modifications to refine RECIST. It put to use vast depository of images and outcomes from various clinical trials which allowed assessment in changes to tumor size based on several formulae.

It compared assessment of 10 lesions with a maximum of 5 in any one organ and compared it with 1,2,3 or 5 organs. Based on this it recommends that 3 lesions may be used and not 5 leading to potentially fewer measurements. It also recommends that the largest lesion be used for measurement as long as the lesion is capable of being measured.

RECIST 1.1 also dealt with lymph nodes in a manner different than what RECIST did. When in RECIST the longest axis of the node was measured and

it had to completely disappear for complete response, in RECIST 1.1, the short axis was measured. A lesion greater than 1.5 cm are suitable for measurement while those smaller than 1 cm are considered as normal. If a node decreases in size almost completely and cannot be measured it is assigned as 5 mm. If it completely disappears it becomes 0 mm. For non-nodal lesions, a lesion more than 1 cm was suitable for measurement. It should be noted here that the short axis of lymph nodes is added to long axis of tumors to calculate overall tumor burden assessment in measurable lesions.

The criteria for progressive disease also underwent a change with RECIST 1.1 – An absolute increase in the sum of tumor dimension of at least 5 mm. This helps to avoid a minimal 20% increase (<5mm) being categorized as progressive disease.

Limitations of Anatomic Response Criteria

Without doubt RECIST and RECIST 1.1 have been used extensively in clinical trials and routine clinical practice but there are various concerns that have not been addressed yet. Amongst them, the greatest concern is the statistical issue of reducing intrinsically continuous data into 4 groups. It is possible that with such grouping and reductionism, potential valuable information that may be critical can get lost. It also fails to recognize the benefit of cytostatic treatments like that for GIST which provides long term stable disease. RECIST is also limited in predicting response to treatment and this has been noted in various clinical trials like SHARP trial for Sorafenib in hepatoma and other trials in

GIST, pediatric tumors and mesotheliomas. There have also been many inter observer variations when RECIST was used. It has also been observed that changes in tumor volume are more suggestive of response and prognosis than one dimensional method of tumor assessment in evaluating tumor response.(71)

Table 3 Comparison between RECIST 1.1, EORTC and PERCIST

Characteristic	RECIST 1.1	EORTC	PERCIST 1.0
Measurability of lesion at baseline	Lesions: longest diameter ≥10 mm; lymph nodes: short axis ≥15 mm	Lesions with high ^{18}F-FDG uptake	SULpeak of baseline lesions at least 1.5-fold greater than liver SULmean + 2 × SD. If liver is abnormal, primary tumour should have uptake >2.0 × SULmean of blood pool
Objective response	CR: disappearance of all target lesions	CMR: complete resolution of ^{18}F-FDG uptake within all lesions, making them indistinguishable from the surrounding tissue	CMR: complete resolution of ^{18}F-FDG uptake within all lesions to a level of less than or equal to that of the mean liver activity and indistinguishable from the background blood-pool levels
	PR: reduction of at least 30 % in the sum of diameters of target lesions	PMR: reduction of at least 25 % in the sum of SUV	PMR: reduction of at least 30 % in SULpeak and an absolute drop of 0.8 SULpeak units
	PD: increase of at least 20 % in the sum of diameters of target lesions or appearance of new lesions	PMD: increase of at least 25 % in the sum of SUV or appearance of new ^{18}F-FDG-avid lesions that are typical of cancer and not related to inflammation or infection	PMD: increase of at least 30 % in SULpeak and an absolute increase of 0.8 SULpeak units
			OR: 75 % increase in TLG, with no decrease in SUL, or appearance of new ^{18}F-FDG-avid lesions typical of cancer and not related to inflammation or infection
	SD: not CR, PR, or PD	SMD: not CMR, PMR, or PMD	SMD: not CMR, PMR, or PMD

METHODS AND MATERIALS

Patients with biopsy proven malignancy of the oral cavity, oropharynx, hypopharynx and laryngopharynx planned for radical treatment with radiation therapy or concurrent chemotherapy or biotherapy with radiation therapy by intensity modulated radiation therapy technique were included in the study. The study period was between February 2017 and March 2018.

Inclusion criteria

- Patients of age more than 18 years
- Patients diagnosed to have biopsy proven Head and Neck cancers of the oropharynx, hypopharynx and laryngopharynx
- Patients undergoing radiation therapy with Intensity Modulated Radiation Therapy (IMRT) with planning PET/CT
- Patients consenting to be a part of the study

Exclusion criteria

- Patients of age less than 18 years
- Patients diagnosed to have any head and neck malignancy other than the primary sites mentioned in the inclusion criteria
- Patients who have undergone surgery for the management of the malignancy

- Patients not consenting to be a part of the study

The study proposal was submitted to institutional review board in September 2016 and the approval from the board after modifications was received in December 2016.

The study included 47 patients from February 2017 to August 2018. The patients were prospectively recruited between February 2017 and March 2018 after an informed consent. Pretreatment all the patients underwent clinical examination, nasopharyngolaryngoscopy (NPL scopy), baseline blood tests and CXR. The patients underwent a planning PET CT and the data from PET and CT was used for volume delineation and treatment planning. The patients underwent radical radiation therapy with or without concurrent systemic treatment with cisplatin or Nimotuzumab. The same patients were followed up and a repeat PET CT scan for response assessment was done after a minimum duration of 10 weeks and response assessment was done by RECIST and PERCIST criteria. They also underwent clinical examination and nasopharyngolaryngoscopy (NPL scopy).

Preparation of participants for PET imaging:

Participants were fasting for more than 8 hours. On the day of scanning blood glucose was measured. Intravenous lines were fixed for all the participants and 7 to 8 mCi of FDG tracer was injected. Participants were waiting in a room with low light, without much physical movement and limited other activities like talking and reading. Imaging was performed after 45 to 70 minutes.

Image Acquisition:

Imaging was performed in Siemens Biograph 6 PET-CT scanner. For head and neck, the number of bed positions used was 3, and if thorax was included along with head and neck, the number of bed positions was increased to 5. The time per bed position was kept as 1.7 min. Iterative reconstruction method called as TrueX provided by the vendor was used with 4 iterations and 21 subsets. The post reconstruction filter used was Gaussian with 4 mm FWHM. Scatter correction and CT based attenuation correction was used. CT data with intravenous contrast was used for attenuation correction for all the participants.

The high voltage used for CT imaging was 130 kVp and the tube current was 80 mAs. If thorax was included, the tube current was increased to 100 mAs. The collimation used was 6 x 1 mm and the field of view (FOV) was 500 mm to 700 mm in axial plane. The scan table was moved linearly with pitch factor 0.8. The X-ray tube and CT detectors were rotated at 0.6 sec/rotation. The scan was performed in caudocranial direction with the participant in head-first position. Filtered back projection algorithm was used for the reconstruction. The reconstruction filter kernel used was B31s medium smooth. The display window for CT was set to the preset mode called as Larynx.

Tumor delineation:

The PERCIST method implemented in this study used the SUVmean value within the tumor. Tumor delineation was an essential step to get SUVmean. Adaptive threshold

segmentation method which we developed in our institution was used for tumor delineation.(72) PET data were transferred to a workstation. Approximate location of the primary tumor was identified and a fiducial was placed. A sphere ROI was drawn around the fiducial and the SUVmax within the ROI was found. The color scale was changed to cold-to-hot and the range of the color scale was adjusted from 0 to the SUVmax which helps to identify the tumor and its margins clearly.

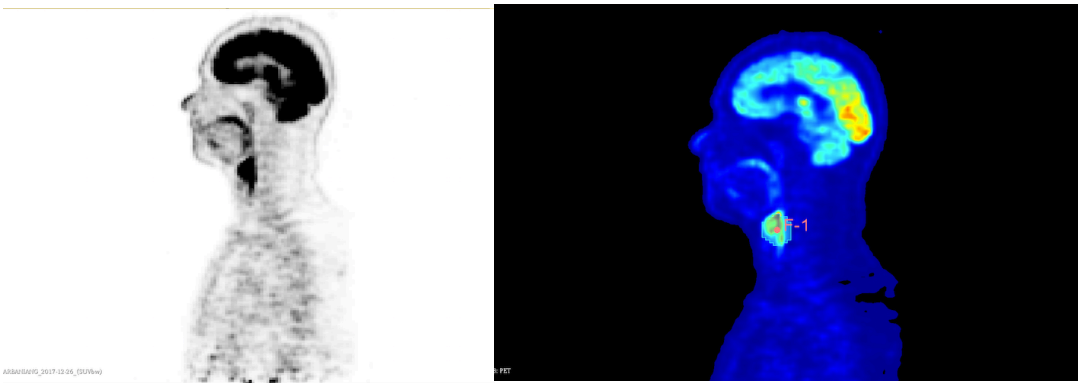

Figure 25 Initial segmentation to identify are with maximum SUV uptake

Another three fiducials were placed around the tumor to represent the background region closer to the tumor but not within the tumor. The SUV values from each background fiducial was taken and averaged to get the local background SUVmean. Initial threshold value for segmentation was calculated from the SUVmax and the mean background value. Initial tumor delineation was performed using the initial threshold value. If the segmented region extends beyond the tumor into the adjacent region, the joining regions were manually erased to disconnect the two regions. The tumor island was retained while discarding the adjacent segmented regions. The initial volume of the tumor was calculated from the initial threshold segmentation region. Final threshold value was calculated using the initial tumor volume, background

SUVmean and tumor SUVmax. The final tumor segmentation was performed using the final threshold value. As mentioned above if any adjacent regions are segmented, they are disconnected manually and removed from the tumor region. The tumor SUVmean and the tumor volume were calculated. Three more fiducials were placed in the liver to calculate the body background SUVmean. All the above-mentioned steps for tumor delineation was performed by a python script based software developed in our institution. The software was incorporated as a module in 3D Slicer which is a open source image processing platform.(73)

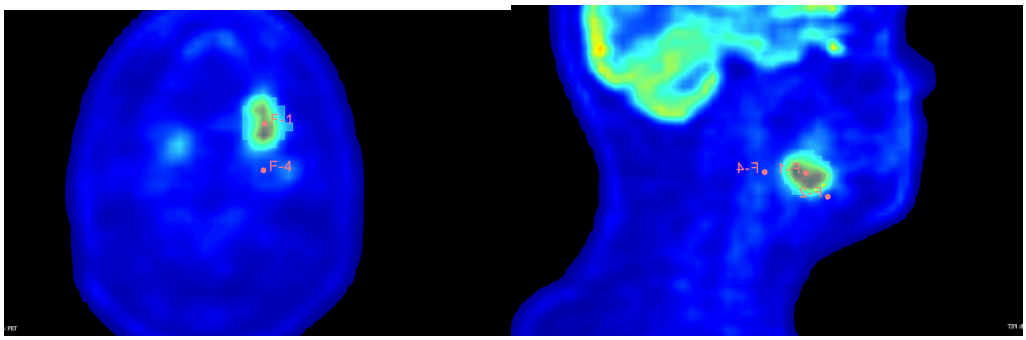

Figure 26 Delineated tumor using adaptive threshold technique

PERCIST response classification:

Height, weight, GRBS value, tumor SUVmean, tumor SUVmax, tumor volume and body background SUVmean of baseline and post treatment imaging were used to calculate PERCIST response. As the body weight based SUV (SUVbw) is influenced by many other parameters (71), lean body mass based SUV (SUVlm) was used for PERCIST classification. Lean body mass was calculated from the height and weight and used to correct the SUVbw to SULlm. Appropriate equations were used to calculate the lean body mass for male and female. In order to reduce the influence of GRBS, SUVlm was further corrected for GRBS to get GRBS corrected SUVlm. And

finally, the body background was subtracted from the GRBS corrected SUVlm. Total lesion glycolysis (TLG) was calculated as the product of tumor volume and corrected SUVlm. PERCIST response classification were done according the criteria given in (68), but we have used corrected SUVlm instead of SUVpeak. PERCIST response classification was also performed using TLG. All the above-mentioned corrections and PERCIST classification were performed by a Libreoffice Calc template. The template was developed earlier as part of a different master degree thesis in our institution. The data was entered into the template for each participant to get the classification based on corrected SUVlm and TLG.

RESULTS

Baseline characteristics

The study was done in 47 patients with primary squamous cell carcinoma in the head and neck region – oral cavity, oropharynx, hypopharynx and laryngopharynx and CUP. There were 44 males and 3 females. The age of the patients varied between 30 and 80 years with a mean age of 56.64 years.

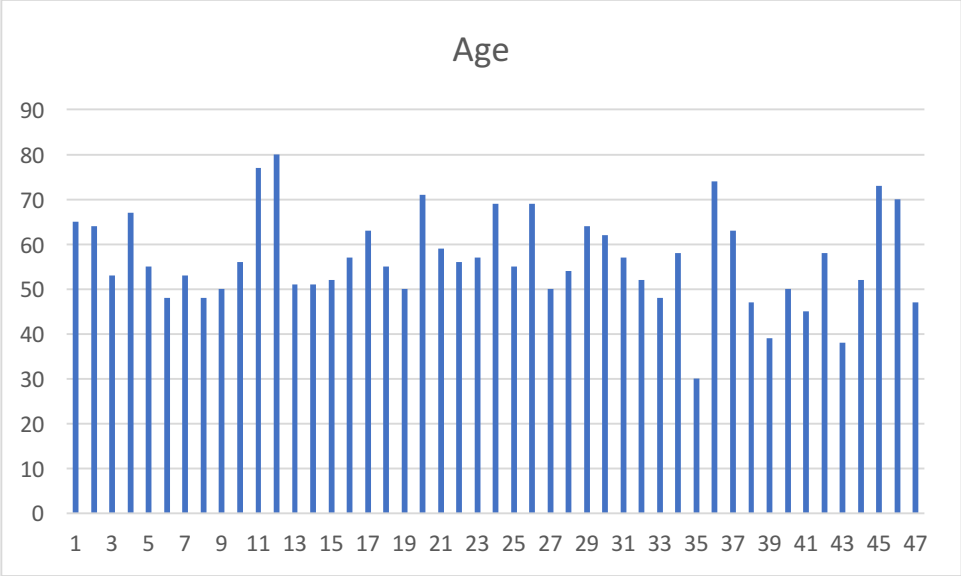

Figure 27 Distribution of age

The most common primary site was oropharynx (15) followed by hypopharynx (14)

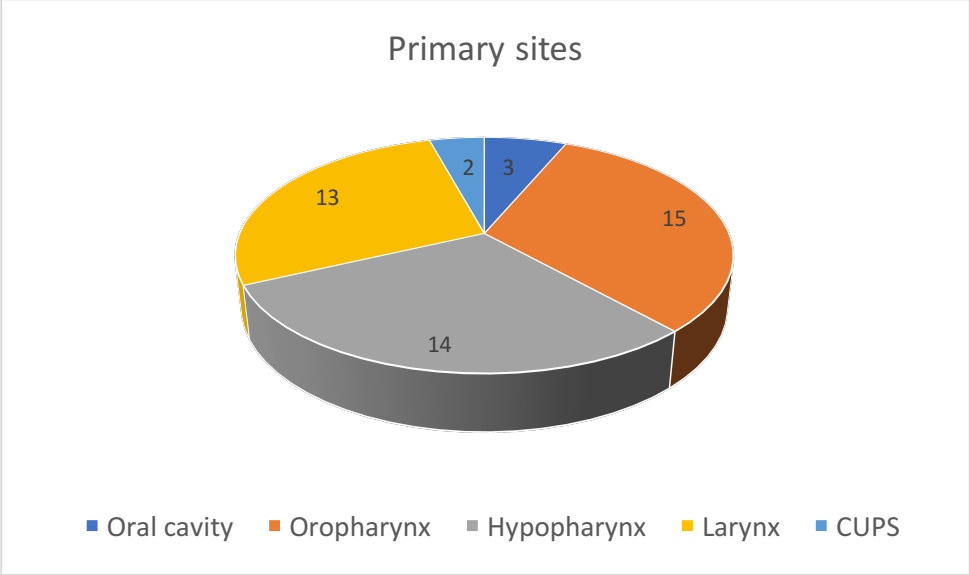

Figure 28 Distribution of primary site

Majority of the patients had locally advanced primary disease with T3 and T4 disease forming 63.8%. Nodal disease was found in 55.3% patients. Stage III disease was seen in 42.6 % and stage IV in 44.7% patients.

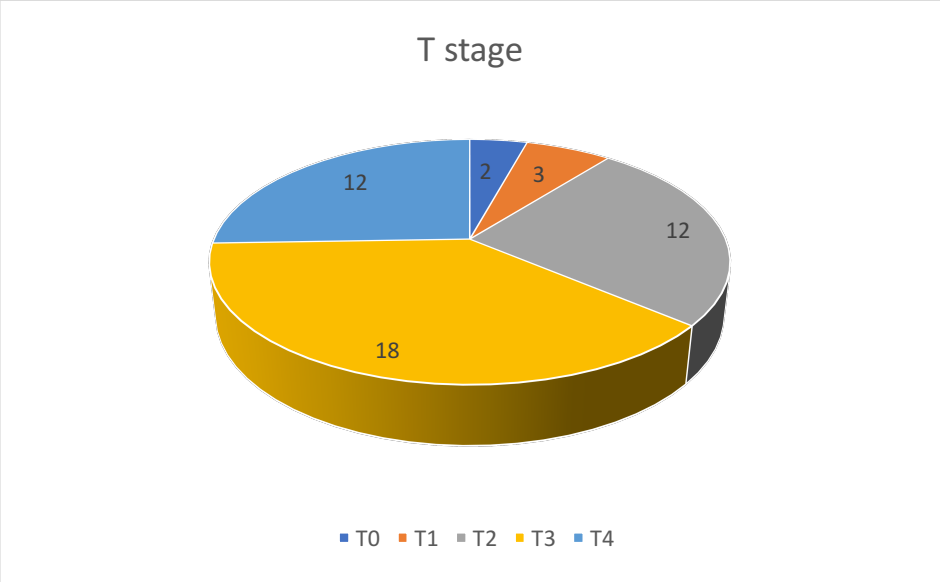

Figure 29 Distribution of T stage

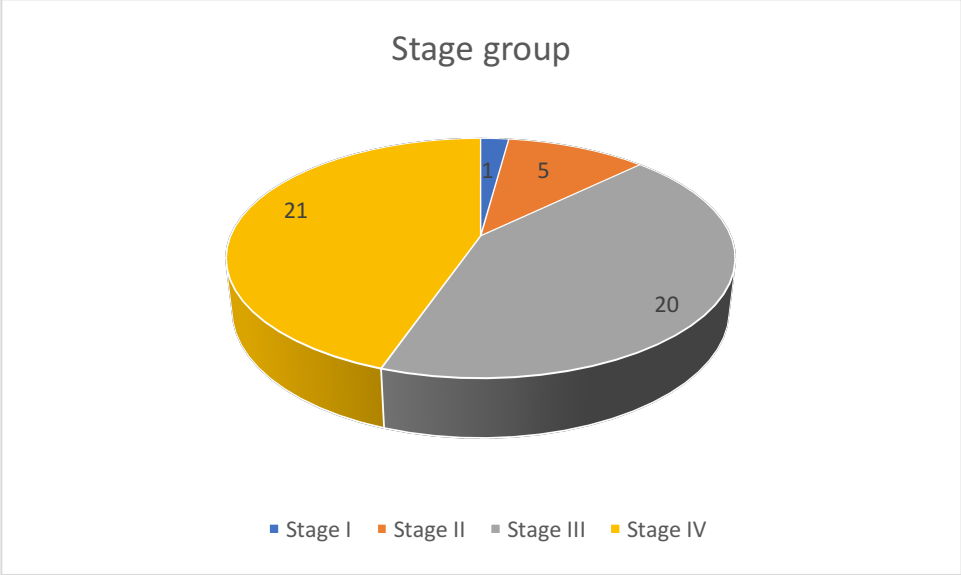

Figure 30 Distribution of stage group

The dose of radiation received varied from 60 Gy to 75 Gy. The concurrent systemic therapy administered was weekly Nimotuzumab, weekly cisplatin and 3 weekly cisplatin and 13 patients (27.7%) did not receive any concurrent systemic treatment.

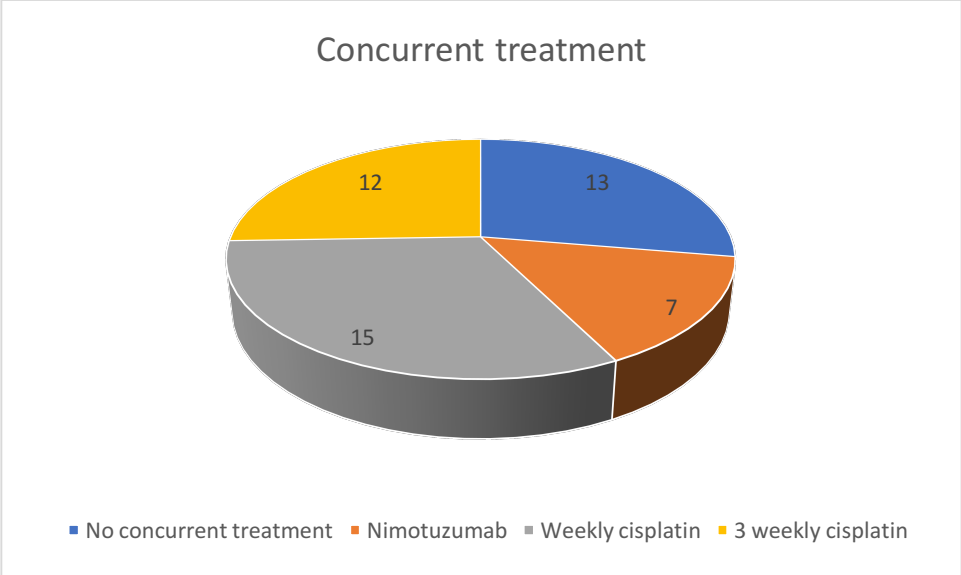

Figure 31 Distribution of concurrent systemic treatment

Induction chemotherapy was administered to 3 patients; 2 of whom received 1 cycle and 1 patient received 3 cycles. The overall treatment time varied between 42 days to 77 days with a mean of 50.32 days. The follow up scan was done after a minimum duration of 70 days (10 weeks) and it ranged from 70 days to 166 days with a mean of 101.37 days. Among these patients, 9 patients were excluded as 1 progressed while undergoing therapy and treatment was converted to palliative radiation therapy; 1 developed cerebrovascular accident after cycle 1 induction chemotherapy and had to undergo surgery for the primary malignancy; 1 patient died due to an unrelated incident and 6 patients were lost to follow up. The baseline or follow up scan data was not retrievable for 2 patients who had completed the study due to data error/ technical glitch. Therefore only 36 patients were included in the final analysis.

The average baseline SUVmax, SUL and TLG for these patients were 18.41 (7.12 to 48.69), 8.09 (1.86 to 23.33) and 87.14 (1.04 to 477.24) respectively.

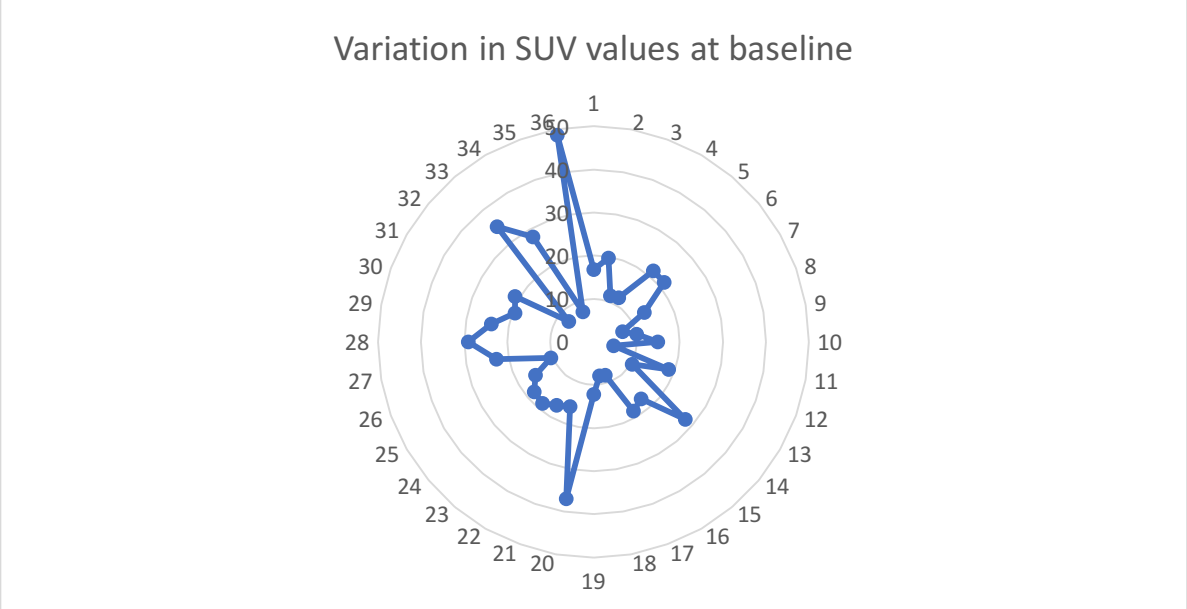

Figure 32 Variation in SUV at baseline

Table 4 Patient characteristics and treatment details

Number of Patients	Total	47
	Male	44
	Female	3
Age (years)	Mean	56.64
	Min	30
	Maximum	80
Primary tumor site	Oral cavity	3 (6.4%)
	Oropharynx	15 (31.9%)
	Hypopharynx	14 (29.8%)
	Laryngopharynx	13 (27.7%)
	CUPS	2 (4.3%)
Stage Grouping	Stage I	1 (2.1%)
	Stage II	5 (10.6%)
	Stage III	20 (42.6%)
	Stage IV A	18 (38.3%)
	Stage IV B	2 (4.3%)
	Stage IV C	1 (2.1%)
Technique and Dose	IMRT	60 Gy – 75 Gy
Concurrent Systemic therapy	No concurrent therapy	13 (27.7%)
	Nimotuzumab	7 (14.9%)
	Cisplatin – weekly	15 (31.9%)
	Cisplatin – 3 weekly	12 (25.5%)
Overall treatment time (days)	Mean	50.32
	Minimum	42
	Maximum	77
Follow up (days)	Mean	101.37
	Minimum	70
	Maximum	166

Comparison of volumes

The volumes of the tumour delineated with PET CT and CT were compared with each other. Figure shows that there was a difference between the volumes obtained with CT and using the adaptive threshold technique using signal to background ratio. The volume obtained using adaptive technique was less than the CT volume.

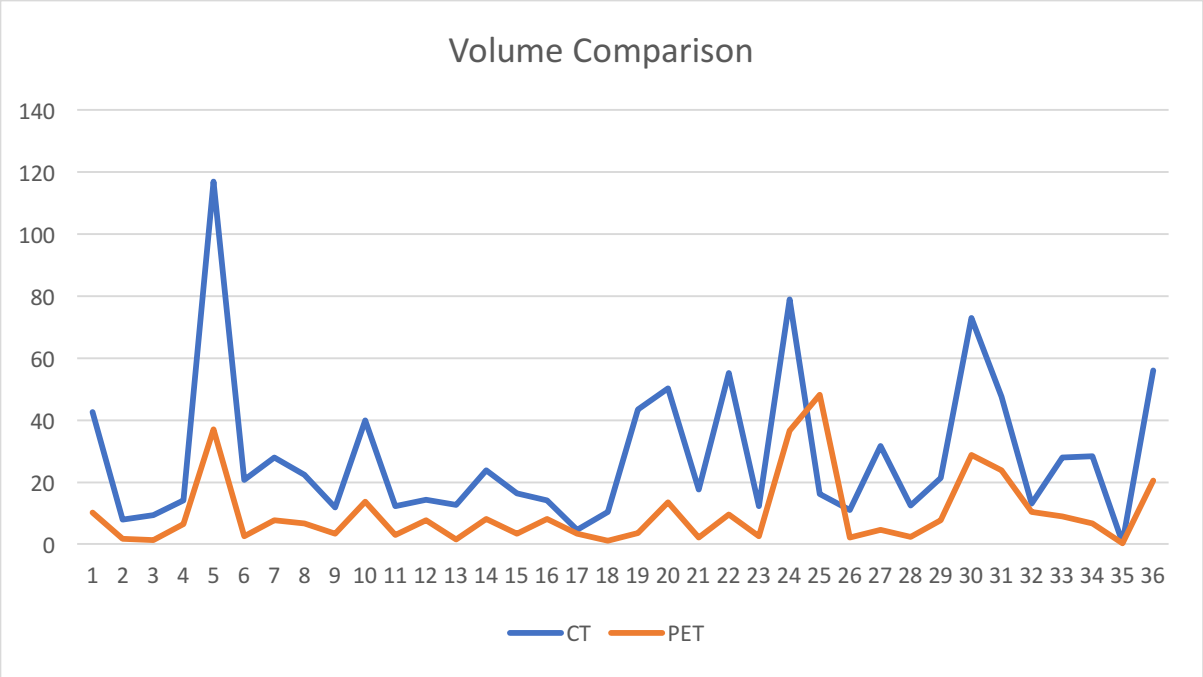

Figure 33 CT and PET CT volume comparison

Response assessment

A total of 36 patients were included in the analysis for evaluation of response.

The overall response and response of primary was assessed separately using clinical examination and NPL scopy, RECIST and PERCIST using 3 different biomarkers (PERCIST SUL, PERCIST TLG and PERCIST SUVmax)

Evaluation of Primary disease

On scopy, findings were described as obvious residual and taken as disease in scopy, mucosal bulge or fullness was taken as abnormal and normal scopy was taken as no disease. Patient with CUP was excluded. Hence finally 35 patients were chosen for this analysis.

SCOPY

Table 5 Response according to NPL scopy and clinical assessment

Normal	27
Disease	6
Abnormal	2
Total	35

RECIST

Table 6 Response according to RECIST

CR	26
PR	3
SD	2
PD	4
Total	35

PERCIST SUL

Table 7 Response according to PERCIST SUL

CMR	7
PMR	26
SMD	2
PMD	0
Total	35

PERCIST TLG

Table 8 Response according to PERCIST TLG

CMR	10
PMR	18
SMD	2
PMD	5
Total	35

PERCIST SUV MAX

Table 9 Response according to PERCIST SUVMAX

CMR	6
PMR	25
SMD	4

PMD	0
Total	35

When the scopy abnormal patients who had only mucosal bulge or fullness were analyzed, they were found to have a decline in SUV of 90% and 80% and were therefore taken as normal for further analysis

Comparison between Scopy and various PERCIST methods used for evaluation of primary

Scopy VS PERCIST SUL

		RECIST				Total
		CMR	PMR	SMD	PMD	
Scopy	Normal	7	21	1	0	29
	Disease	0	5	1	0	6
Total		7	26	2	0	35

Scopy vs PERCIST TLG

		RECIST				Total
		CMR	PMR	SMD	PMD	
Scopy	Normal	10	17	0	2	29
	Disease	0	1	2	3	6
Total		10	18	2	5	35

Scopy vs PERCIST SUV MAX

		RECIST				Total
		CMR	PMR	SMD	PMD	
Scopy	Normal	6	22	1	0	29
	Disease	0	3	3	0	6
Total		6	25	4	0	35

Scopy was compared with the 3 methods of calculating PERCIST. A total of 29 patients had a normal scopy and only 6 had abnormal scopy. Using PERCIST TLG maximum number (10) had complete response on PERCIST and normal scopy.

Comparison between scopy and CT by RECIST

		RECIST				Total
		CR	PR	SD	PD	
Scopy	Normal	24	2	1	2	29
	Disease	2	1	1	2	6
Total		26	3	2	4	35

Majority of the patients with normal scopy had complete response by RECIST.

Scopy and RECIST Complete Response

Further analysis was carried out to look at the metabolic response among the patients who had complete response on Scopy and RECIST. The average decline in SUL, TLG and SUVmax for these patients were 90.3% (-185.56% to -22.78%), 62.7% (-101% to 354.7%) and 69.5% (-100% to -12.8%) respectively. Best correlation was seen with the SUL method.

In the PERCIST SUL criteria for this subset of patients, 17 patients had a partial metabolic response with an SUL decline of 81.21% (-96.01% to -41.31%), 6 patients had complete metabolic response with an average decline of 126.81% (-185.56% to -100%).

In the PERCIST SUV MAX criteria for this subset of patients, 18 patients had a partial metabolic response with an SUVmax decline of 64.3%(-88.6% to -36.7%), 5 patients had complete metabolic response with an average decline of 100%.

In the PERCIST TLG criteria for this subset of patients, 14 patients had a partial metabolic response with a TLG decline of 78.77% (-98.6% to -51.2%), 8 patients had complete metabolic response with an average decline of -99.89% (-101% to -99%).

Scopy positive subset

Scopy positive patients were analyzed. A total of 6 patients were in this group. By RECIST 2 had progressive disease, 1 had stable disease, 1 had partial response and 2 had complete response. The average change in SUL, TLG and SUV max for these patients were decrease of 56.55% (-89.19% to 25.95%), increase by 84.66% (-93.89% to 321.4%) and decrease by 31.29% (-70.6% to -0,73%). Among these patients 5 had PMR in the PERCIST SUL and they had a decline in SUL of 73.05% (-89.19% to -58.95%). Best correlation was seen with the SUL method.

Scopy negative CT equivocal subset

Analysis of Scopy negative CT equivocal subset was also done. The average decline in SUL, TLG and SUVmax for these patients were 89.08% (-185.56 to -22.78%), 68.41% (-100% to 354.7%) and 70.14% (-100% to -12.8%) respectively.

In the PERCIST SUL criteria for this subset of patients, 21 patients had a partial metabolic response with a decline of 80.76% (-96.01% to -41.3%). 7 patients had complete metabolic response with an average decline of 122.98% (-185.56 to -100%).

In the PERCIST SUV MAX criteria for this subset of patients, 22 patients had a partial metabolic response with a decline of 64.6% (-88.6% to -36.7%).

In the PERCIST TLG criteria for this subset of patients, 18 patients had a partial metabolic response with a decline of 81.24% (-98.6% to -51.2%).

Best correlation was seen with the SUL method.

Comparison of RECIST with the three PERCIST methods

All 36 patients were used for this analysis and it compared both primary and nodal disease.

RECIST vs PERCISTSUL

		CMR	PMR	SMD	PMD	TOTAL
	CR	4	21	1	1	27
RECIST	PR	0	3	0	0	3
	SD	0	2	0	0	2
	PD	0	1	1	2	4
TOTAL		4	27	2	3	36

In RECIST and PERCIST SUL criteria, a 4 CMR had CR on RECIST. The 21 PMR were also CR in RECIST. The 3 patients with PMD, 2 of them had PD in RECIST. 2 patients with SMD, one was CR and the other was PD. Among the 27 patients with

partial metabolic response (PERCIST-SUV), the average decrease in SUV was 82.26%. The decrease in SUV ranged from 41.3% to 96.01%. Majority (59%) of the patients had a decrease more than 85% and 74% had a decrease more than 80%.

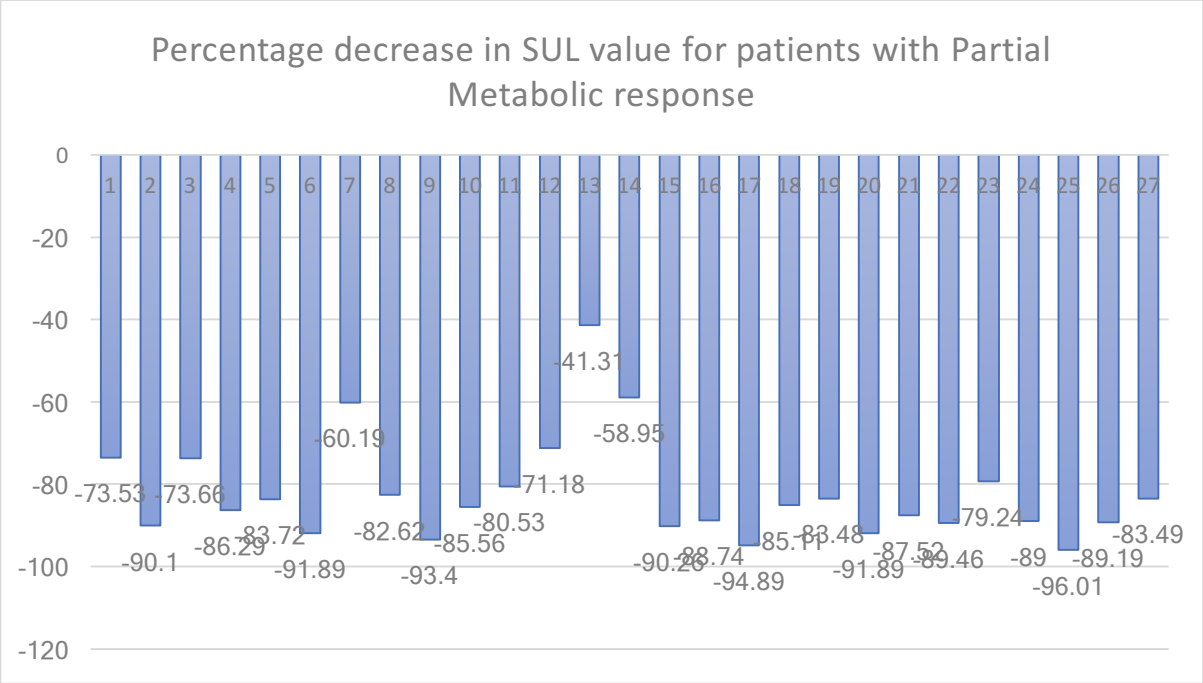

Figure 34 Percentage decrease in SUV value in patients with partial metabolic response

RECIST vs PERCIST TLG

		CMR	PMR	SMD	PMD	TOTAL
	CR	5	20	0	2	27
RECIST	PR	0	3	0	0	3
	SD	1	0	1	0	2
	PD	0	0	1	3	4
TOTAL		6	23	2	5	36

In RECIST vs PERCIST TLG, all 4 CMR were in CR by RECIST. The 20 PMR patients were CR and 3 PMR were in PR group by RECIST. One patient with SMD was in PD group in RECIST. Both patients with PMD were in CR group in RECIST. The progressive metabolic disease group by PERCIST TLG group did not correlate well with the scopy, RECIST and other PERCIST groups.

RECIST vs PERCIST SUVMAX

		CMR	PMR	SMD	PMD	TOTAL
	CR	4	21	2	0	27
RECIST	PR	0	3	0	0	3
	SD	0	2	0	0	2
	PD	0	2	2	0	4
TOTAL		4	28	4	0	36

In RECIST vs PERCIST SUV MAX, all 4 CMR were in CR by RECIST. The 28 PMR patients were 21 CR, 3 PR and 2 SD and 2 PD by RECIST. Four patients with SMD 2 was in PD group and 2 in the CR group in RECIST. There were no patients with PMD.

All the patients with complete metabolic response belonged to complete response in RECIST emphasizing the high negative predictive value of PET. Most patient in PMR by the three methods belonged to CR group in RECIST.

MTV, TLG and SUV max as predictive biomarkers.

The baseline TLG for the patients who had complete metabolic response was 27.3cc. The baseline TLG for partial metabolic response patients was 97.27cc.

The prognostication predictive biomarkers viz; MTV and TLG were analyzed for each PERCIST SUL subset. Change in SUVmax was also analyzed for the same SUL subset.

Table 10 Change in MTV, TLG and SUVmax compared to baseline

	MTV change	TLG change	SUVmax change
CMR	-100%	-100%	-100%
PMR	186.78cc	-57.54%	-67.27%
SMD	224.02cc	+164.6%	-6.76%

Since progressive metabolic disease patients included patients who developed new lesions it was not included for this analysis. All the patients with complete metabolic response had a decline in MTV, TLG and SUVmax of 100%. The progressive metabolic response had a decline on TLG and SUV max of 57.54% (-99.15% to 321.36%) and 67.27% (-88.6% to -3.82%) respectively. The patients with stable metabolic disease had an increase of TLG by an average of 164% (-25.5% to 354.72%) and decrease in SUVmax of only 6.76% (-12.8 to -0.73%).

MTV revealed that patients with stable metabolic response had a higher volume change (224.02cc) compared to partial metabolic response (186.78cc) and complete metabolic response. The discordancy could be due to residual post RT inflammation and edema resulting in a higher volume.

DISCUSSION

The purpose of this prospective study was to study the role of ^{18} FDG PET CT in head and neck squamous cell carcinomas - the diagnostic utility, role in radiation planning and to assess response to radical radiation therapy with or without concurrent systemic treatment using PERCIST after completion of treatment.

Role in identification of clinically and CT wise unknown primary and negative neck nodes.

The diagnostic accuracy of PET CT including its high sensitivity and usefulness in identification of carcinoma unknown primary with cervical nodal metastasis has been reported in literature.(47,48,50,51) Our study had 3 patients with carcinoma unknown primary with cervical nodal metastasis. With the help of PET, the primary of one of these three patients were identified as oropharynx. In a meta-analysis done by Rusthoven et al (74,75) FDG PET was able to identify primary in 24.5% patients for whom primary was unidentifiable following routine investigations. In patients who were clinically node negative, PET CT was helpful in identifying positive nodes. The radiologist also expressed the utility of PET CT when the nodes were equivocal on routine CT imaging but had tracer uptake in the PET scan. We had a patient who was upstaged as metastatic disease due to lung metastasis detected by PET-CT. This finding led to the patient getting systemic treatment upfront instead of concurrent chemoirradiation planned earlier. Tantiwongkosi et al (76)and Goel et al (48) described high sensitivity and specificity of PET CT in detecting lung metastasis.

Role in volume delineation

PET has also been helpful in accurate volume delineation during RT planning. The PET images were taken in treatment position with immobilization and was automatically co-registered with the CT images. Literature reports that PET CT is useful in identifying accurate tumor volume compared to CT and MRI and most studies report the smallest GTV volume as the one identified by PET CT. (56,58,59) Kishan et al mentions the various methods used for delineation of tumor volume and the differences between them. (59)

Historically most common method utilized for identification of tumor volume was by visual interpretation. The other methods were to identify the area of maximum SUV uptake and uniformly expanding it by a fixed margin or threshold to calculate the tumor volume. These methods did not account for the anatomic structures in the surrounding area or was subject to variation due to the difference in window levels from user to user and institution to institution. Another method called signal to noise ratio could overestimate GTV due to longer range of the positron in air cavities. In the present study, an adaptive threshold technique was utilized for identifying tumor volume which took into account the background metabolic activity to accurately delineate the tumor. Our data concur with the reported data and we found that our PET CT contoured GTV using adaptive threshold was smaller than that contoured with CT alone. Some studies have explored the scope of dose painting and dose escalation and de-escalation based on metabolic imaging parameters (60,77) but that was beyond the scope of our present study.

Role of PET-CT biomarkers

Role of biomarkers at baseline

The various PETCT biomarkers at baseline can be used for prognostication. Our study had a mean SUVmax, mean SUL and mean TLG at baseline of 18.41, 8.09 and 87.14 cc respectively. The baseline TLG for complete metabolic responders was 27.3cc compared to 97.27cc for partial metabolic responders. This suggests that TLG could be used as a prognostic marker, a lower value being an indicator of better response to treatment. Koyazu et al (78)in their study had proved that an SUVmax >10 and TLG >70 cc was associated with negative effect on disease specific survival and disease-free survival. In another study by Torizuka et al(64), it was demonstrated that SUVmax <7 predicted a better 2-year local control and disease-free survival. The high SUVmax, SUL and TLG value in our study could be suggestive of more aggressive disease in our patients (87.3% had stage 3 or 4 disease) and further follow up needs to be done to see the outcome among these patients. This could also be one of the reasons for high rate of partial metabolic responders when PERCIST was used for assessment in these patients.

Role of biomarkers for response assessment

To negate the low positive predictive value of PET, it was hypothesized that TLG which incorporated the metabolic tumor volume and SUVmean could be a more comprehensive method to assess response since in addition to metabolic information, it also included a volumetric parameter. The decline in TLG for patients with CMR was 100% and for patients with PMR was 57.54%. The SMD patients had an increment of 164% which correlated well with the responses seen. Usmanji et al

(79)in their study showed that a decrease in TLG more than 34% compared to baseline was suggestive of a good response. Since our partial metabolic responders had a decline in TLG greater than what was reported in literature we expect them to have good response if followed up for a longer time. Change is SUVmax was also concordant with the change in TLG and response.

Response assessment

Ideal time to do follow up PET

Response assessment after completion of treatment was done by clinical examination and PET CT. Historically various authors have attempted doing the follow up imaging as soon as 1 month post treatment to as long as 1 year. Greven et al (80) did serial PET scans at 1, 4, 12 and 24 months after treatment and was able to demonstrate that scans done after 1 month had high specificity of 95% but poor sensitivity of 59%. But the scan done at 4 months had high sensitivity (100%) and specificity (90%). The reason for poor sensitivity was radionecrosis, acute concomitant infection, benign polyps and post radiation inflammation or mucositis.(81) The current recommendation on optimal duration post treatment for PET CT scan is based on the work by Helsen et al (62,82) who demonstrated that diagnostic performance increases until 11 weeks and then it plateaus thereafter. Our study also followed a similar protocol and the mean duration to response assessment PET CT post treatment was about 14 weeks. Shortest duration was 10 weeks and longest was 23.7 weeks.

Response assessment – PERCIST

We compared response assessments for primary done by clinical examination and NPL scopy with RECIST and 3 variants of PERCIST; utilizing SUV lean body mass corrected for glucose and background (SUL), total lesion glycolysis and SUV max. There was poor correlation between the clinical examination, scopy, RECIST and PERCIST findings.

Complete metabolic responders

Among our patients, all the patients with complete metabolic response by all 3 methods did not have any disease on clinical examination, scopy and RECIST suggesting a high negative predictive value.

The meta-analysis and prospective study from India by Gupta et al (67,83) on PET CT, demonstrated a high specificity of 87.5% and 91.8% and negative predictive value of 95.1% and 91.8%. but what was more striking was the poor sensitivity – 79.9% and 50% and poor positive predictive value – 58.6% and 50%. A negative PET scan was highly suggestive of absence of disease but a positive PET scan was not a definite proof of presence of disease. The study by Chen et al (81) also reported similar poor positive predictive value and had high false positive rate. They reported that contrast enhanced CT was superior to PET CT in specificity and PPV at primary site. A study by Malone et al (84) to identify early prediction of response comparing PET CT with CT also observed that a negative PET CT accurately determined response and did not require surgical intervention where as positive PET warrants further evaluation in view of false positive results. Similar conclusion was observed

by Passero et al (85,86) who looked into RECIST criteria versus combined PET CT scan.

Partial metabolic responders

Majority of our patients had partial metabolic response by PERCIST, while on the evaluation with RECIST and scopy they had CR. The reason for not getting a complete resolution of SUV uptake in them, which is the recommendation for calling it a CMR may be due to probable residual disease, post RT inflammation or infection.

Further analysis that was carried out among our patients with PMR looking at decline in SUV, showed that majority of them had a decline in SUL more than 85% compared to baseline, suggesting good response to therapy and probably complete response and those with a lower change may be having residual disease. Follow up assessment of these patients will be required for confirmation of this correlation between decline in SUV and response. In a study by Lowe et al (65) where they looked at change in SUV as a surrogate to response they found that the mean SUV change between pre and post therapy PET scan was 34% % in patients with residual disease and 82% in patients having pathologically complete response.

Response assessment scopy evaluation was reported as bulge and fullness in two patients. The SUL data for these two patients were analyzed and it showed a decline of 90% and 80% and this helped us to identify these patients as normal.

One of the patients who had a residual disease on scopy in the form of ulceration had partial metabolic response according to PERCIST SUL with a drop in SUL of

89.19%. He underwent biopsy from the suspicious lesion which was reported as chronic inflammation suggestive of post RT changes.

The patients who had a normal scopy and incomplete metabolic response were analyzed. In this group of patients, the decline in SUL, TLG and SUVmax in partial metabolic responders were much higher than the decline observed for stable metabolic disease or progressive metabolic disease. It was also noted that the decrease in SUL was maximum when compared to TLG and SUVmax which suggests that SUL was a good biomarker for response assessment since it correlated well clinically. Since there was a better correlation with the change in SUL as compared to TLG and SUVmax in our study this could be considered as the ideal method to assess response.

The patients who had residual on scopy were found to have much lower decline in SUL, TLG and SUVmax compared to the scopy normal group suggesting that lower decline in these biomarkers correlate with a poor response.

Comparison of PERCIST with RECIST

PERCIST was also compared with RECIST criteria which was taken as the established gold standard for response assessment. All 4 patients with complete metabolic response belonged to complete response by RECIST suggesting 100% concordance and of the 3 patients with progressive metabolic disease, 2 belonged progressive disease by RECIST suggesting 66% concordance. The data by Passero et al (85,86) had reported concordance between CT and PET of 62%, clinical exam and CT of 43% and clinical exam and PET of 51%. The patients who had CMR was

normal on scopy and had complete response by RECIST. This reemphasized the high negative predictive value of PET CT. The addition of PERCIST was helpful in identification of PMD in a patient reported as complete response by RECIST. The senior radiologist who reported RECIST felt that the addition of PET scan gave more confidence in reporting residual post treatment, as there would be an ill-defined soft tissue mass in the area of the disease on a CT scan, which would be too difficult to quantify and distinguish from surrounding normal tissue.

MTV and SUVmax for response assessment

MTV was a poor biomarker for response as the post treatment response assessment scans had a large volume of very small FDG uptake most likely due to post RT inflammation and edema and hence it did not correlate well with the response seen. SUVmax correlated well with the response seen but it was not considered as a good biomarker to assess response as it considered the uptake in only one pixel and did not consider the tumor as a whole. The only benefit of SUVmax was its reproducibility.

CONCLUSION

The addition of PET to CT for imaging head and neck squamous cell carcinomas was found to be beneficial for diagnosis, staging, radiotherapy planning and response assessment.

Total lesion glycolysis was identified as a predictive biomarker. A low baseline low TLG was predictive of better response to treatment.

Change in PET CT biomarkers especially SUL has good correlation with response and therefore can be considered as a surrogate for response. Change in MTV was a poor surrogate for response.

A patient with an abnormal scopy report can be kept on close follow up if the decrease in PET CT biomarkers (SUL, SUVmax and TLG) is significant.

A positive PET scan can be followed up with serial imaging if the clinical suspicion of residual or recurrent disease is low and if the PET CT biomarkers (SUL, SUVmax and TLG) show a significant decline.

A negative PET was suggestive of absence of disease and it had a high concordance with RECIST, clinical examination and scopy

LIMITATIONS

Our study had a small sample size and did not have enough number of patients to bring out the significant results.

HPV analysis was not done for oropharyngeal primary which was the majority in our patient population. HPV positive patients are relatively radioresistant and takes a longer time to clear peri-tumoral inflammation due to its immunomodulatory mechanism.

The time to follow up scan was 12 weeks. It could have helped to do the scan later than 12 weeks allowing for edema and inflammation to decrease.

We did not have a uniform PET CT imaging protocol and this could have resulted in variations in the values obtained for calculating results.

There is a possibility for change in SUV from software to software. Reproducibility is difficult. There could be inter observer variation in the delineation of tumor from normal surrounding tissue.

Study didn't account for follow up scan or surgical intervention for abnormal response on response assessment scan. Hence identification of true positives was not feasible.

Histopathology correlation for abnormal PET-CT findings was not done.

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ANNEXURES

INFORMED CONSENT

Informed Consent Form

Christian Medical College, Vellore

Department of Radiation therapy

Comparison of various imaging modalities for target volume delineation, treatment response assessment using PERCIST criteria and prognostication algorithm for predicting response to treatment in Head and Neck cancers

Study Number: _____

Subject's Initials: _____Subject's Name: _____

Date of Birth / Age: _____

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I understand that the investigation being done (planning PET CT) may reveal findings that might not have been present in the staging CT scan which might delay initiation of treatment, require further invasive investigations or result in a different mode of treatment altogether. [ ]

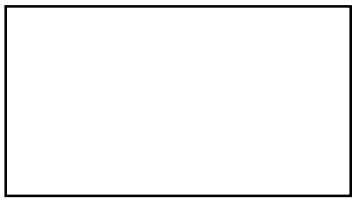
(v) I understand that I will have to bear the expense of additional investigations (partly or wholly) that may become necessary in light of the findings of the investigation

done (planning PET) to confirm diagnosis. [ ]

(vi) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(vii) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject.



Date: _____/_____/_____

Signatory's Name: _____

Signature or thumb impression of representative

Representative: _____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature or thumb impression of the Witness: _____

Date: _____/_____/_____

Name & Address of the Witness:

INFORMATION SHEET AND CONSENT FORM

Christian Medical College, Vellore

Department of Radiation therapy

Comparison of various imaging modalities for target volume delineation, treatment response assessment using PERCIST criteria and prognostication algorithm for predicting response to treatment in Head and Neck cancers

Patient's Information sheet

You are being requested to participate in a study which aims to compare difference in metabolic tumor volumes created using PET-CT when same is used for simulation and planning for radiation therapy in head and neck cancers before and after completion of treatment.

What does this study do?

This is an observational study to compare the metabolic tumor volume differences seen before and after completion of treatment in head and neck cancers. In this study,

the volume delineation for radiation therapy will be done by two different modalities of imaging ie CT and PET/CT. If your tumor is such that it is not FDG avid due to hypoxia or any other factors you will undergo a diffusion weighted MRI. We will compare the volume difference when we use these two different methods. You will undergo a similar repeat imaging 3 months after completion of your treatment. This will help us to evaluate treatment response and prognosticate regarding risk of recurrence. This study may also give us an insight into which areas of head and neck malignancies should be planned and treated with higher dose based on the dosimetric analysis.

Does this study have any side effects?

This is an observational study with no particular side effects. You will undergo a planning

PET/CT scan following which target volume delineation will be done with CT and PET/CT. If your tumor is such that it is not FDG avid due to hypoxia or any other factors you will undergo a diffusion weighted MRI. For your treatment GTV is delineated on CT will be performed according to current clinical protocols and treatment will be carried out on current standard clinical guidelines. 3 months after treatment you will undergo a second PET-CT and treatment response assessment will be done by delineating anatomic and metabolic tumor volume.

If you take part what will you have to do?

If you agree to participate in this study, you will only have to sign the consent form. The

volume delineation, planning and dosimetric analysis will be done by the Radiation Oncologist with the help of Medical Physicist. There will be no change in your treatment

and will be as per the standard.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

Since this is an observational study, no particular study related side effects are expected.

Will you have to pay for the study?

This is an observational study and there is no change in the standard treatment of care. You need not pay anything more than the regular treatment charges as applicable for the radiation therapy and the chemotherapy.

What happens after the study is over?

You will be advised to have regular checkups at the specified intervals as advised which

will be every 3 months in the first one year, every six months for the next two years and

yearly thereafter.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical

notes may be reviewed by people associated with the study, without your additional permission.

If you have any further questions, please ask ----------, Ph No: ----------, email: ----------

DATA COLLECTION PROFORMA

Case No: RT No:

Name: Age:

Hospital Number: Sex:

Address:

Occupation:

Phone number:

Presenting complaints:

History of presenting illness: Symptom Yes/No Duration

1. Throat pain
2. Cough
3. Hoarseness of voice
4. Dyspnoea
5. Stridor
6. Headache
7. Neck swelling
8. Ulcer
9. Dysphagia
10. Others

Past history:

Associated diseases: Premalignant conditions

DM/HTN/Pull TB/Others

Allergies

Prior malignancy

Prior surgery

Prior major illness

Addictions: Smoking

Other tobacco products

Alcohol

Drug history:

Treatment history:

Family history:

PHYSICAL EXAMINATION

Performance Status: ECOG 0 / 1 / 2 / 3 / 4

Pallor

Icterus

Cyanosis

Clubbing

Lymphedema

Yes/No

Tracheostomy

Ryle's tube

Height: _____ cm Weight: _____ kg

BSA: _____ m2

SYSTEMIC EXAMINATION

Respiratory system:

Cardiovascular system:

Per abdomen:

LOCAL EXAMINATION

Oral cavity:

Mouth opening:

Tongue movements:

Teeth:

Oral hygiene:

Lips:

Buccal mucosa:

Alveolus:

GB sulcus:

Retro molar trigone:

Tonsillar fossae:

Others:

Neck

Thyroid

de	Level	Number	Size	Mobile/ Fixed	Discrete/ Matted	Skin – Free/Tethered/Ulcerated
	1a					
	1b					
ght	2					
	3					
	4					
	5					
	1a					
ft	1b					
	2					
	3					
	4					
	5					

Nodes

NPL Scopy / IDL scopy:

Baseline

Follow up and TSH

CLINICAL DIAGNOSIS:

T N M

Stage:

Biopsy:

Number:

Squamous Cell Carcinoma / Adeno-squamous carcinoma Well differentiated / Moderately differentiated / Poorly differentiated

MDT decision

RT Dose and Fraction

Systemic treatment

Number of cycles

Overall treatment time

Follow up duration

CT scan:

Volume

CR

PR

SD

PD

PET

Scan 1		Scan 2	
Date		Date	
SUV max		SUV max	
SUV mean		SUV mean	
Volume		Volume	
TLG		TLG	

Change in SUV

Change in TLG

PERCIST

CMR

PMR

SMD

PMD

Name	Hospital Num	Age	Sex	Primary	PET1	Stage	Stage gp	RT dose	Chemotherap	Start date	Completed date	OTT	PET 2	F/U	
Gunraj Steph	687582G	65	Male	BoT	13.02.2017	T4N2cM0	III	70Gy in 35	Fr	Nimotuzumal	02/03/17	20/04/17	49	18/07/17	89
Md Alauddin	762762G	64	Male	Glottis	13.03.2017	T3N0	III	70Gy in 35	Fr	Nimotuzumal	24/03/17	17/05/17	54	26/07/17	70
Tarrendro Di	550982G	53	Male	Supraglottis/	30.03.2017	T2N0/T1N0	II	70Gy in 33	Fr	Nil	06/04/17	23/05/17	47	12/09/17	112
Kerson Sangr	793886G	67	Male	Pyriform Sin	13.03.2017	T2N0	II	70Gy in 35	Fr	Nil	24/03/17	11/05/17	48	07/09/17	119
Ranjan Sengu	832101G	55	Male	Pyriform Sin	12.04.2017	T4bN2cM0	IVB	70Gy in 33	Fr	Weekly Cispl	20/04/17	05/06/17	46	07/09/17	94
Abdul Gani	804236G	48	Male	Supraglottis	17.03.2017	T3N2cM0	IVA	63Gy in 35	Fr	IC x1 + Week	13/04/17	01/06/17	49	06/10/17	127
Ishwar Prasa	877467G	53	Male	Supraglottis	31.05.2017	T3N0	III	70Gy in 35	Fr	Nimotuzumal	12/06/17	04/08/17	53	15/01/18	164
Murali K	721444D	48	Male	Supraglottis	01.06.2018	T2N0	II	70Gy in 33	Fr	Nil	01/06/17	18/07/17	47	16/10/17	90
Anoop Kuma	186878B	50	Male	Soft Palate	11.05.2017	T2N0	II	66Gy in 30	Fr	Nil	05/06/17	17/07/17	42	23/10/17	98
Sylvanus Mar	553739G	56	Male	Hypopharynx	1.05.2017	T4bN2bM0	IVB	70Gy in 35	Fr	Weekly Cispl	02/05/17	20/06/17	49	22/09/17	94
Pappi Thoma	890754G	77	Male	Hypopharynx	12.06.2017	T2N2bM0	IVA	70Gy in 35	Fr	Nimotuzumal	20/06/17	05/08/17	46	26/10/17	82
Mst Saleha	907200G	80	Female	Oropharynx	10.07.2017	T2N2bM0	IVA	70Gy in 35	Fr	Weekly Cispl	20/07/17	12/09/17	54	02/01/18	112
Khokan Ghos	911441G	51	Male	Pyriform Sin	12.07.2017	T2N0	II	70Gy in 35	Fr	Nil	25/07/17	14/09/17	51	21/12/17	98
Md Akter Ho	950170G	51	Male	CUPS	28.07.2017	T0N1M0	II	70Gy in 35	Fr	3 weekly x 2	29/08/17	17/10/17	49	19/03/18	153
Ranjit Dey	948113G	52	Male	Supraglottis	16.08.2017	T2N1M0	III	70Gy in 33	Fr	3 weekly x 2	24/08/17	09/10/17	46	03/01/18	86
Mohammad	928837G	57	Male	Glottis	17.08.2017	T3N0M0	III	70Gy in 33	Fr	Nil	30/08/17	13/10/17	44	19/01/18	98
Alhaj	917327G	63	Male	Glottis	28.08.2017	T3N0M0	III	70.2Gy in 33	Nil		06/09/17	20/10/17	44	04/04/18	166
Prodip Ranja	991110G	55	Male	Oropharynx	10.10.2017	T2N2M1	IVC	70Gy in 35	Fr	Weekly Cispl	29/01/18	28/03/18	58	10/01/18	-77
Subodh Adhil	978893G	50	Male	Glottis	18.10.2017	T3N0M0	III	70Gy in 35	Fr	3 weekly x 2	26/10/17	13/12/17	48	13/03/18	90
Noel Stone	571785G	71	Male	Soft Palate	20.10.2017	T3N0M0	III	70Gy in 35	Fr	Nimotuzumal	30/10/17	18/12/17	49	06/04/18	109
Harish Chanc	989849G	59	Male	Tongue	27.10.2017	T4aN2bM0	IVA	70Gy in 35	Fr	Weekly Cispl	07/11/17	05/01/18	59	06/04/18	91
Budha Bhatt	013254H	56	Male	CUPS	15.11.2017	T0N2N0	III	66Gy in 33	Fr	3 weekly x 2	23/11/17	22/01/18	60	06/04/18	74
Ranajit Kuma	024633H	57	Male	Hypopharynx	14.11.2017	T2N1M0	III	70Gy in 35	Fr	3 weekly x 2	27/11/17	12/02/18	77	11/05/18	88
Medayil Alex	034350H	69	Male	Oropharynx	17.11.2017	T3N1M0	III	70Gy in 35	Fr	Nimotuzumal	27/11/17	19/01/18	53	17/04/18	88
Gnanaselvi	038589H	55	Female	Pyriform Sin	24.11.2017	T3N0M0	III	70Gy in 35	Fr	Weekly Cispl	05/12/17	29/01/18	55	02/05/18	93
Kanniyappan	160439B	69	Male	Tongue	27.11.2017	T4N2M0	IVA	66Gy in 33	Fr	Nil	04/12/17	19/01/18	46	09/04/18	80
Shaji Varghe	048746H	50	Male	Oropharynx	28.11.2017	T1N2bM0	IVA	70Gy in 35	Fr	Weekly Cispl	05/12/17	29/01/18	55	04/05/18	95
Uttam Pal	031161H	54	Male	Pyriform Sin	29.11.2017	T3N0M0	III	70Gy in 35	Fr	Weekly Cispl	07/12/17	27/01/18	51	25/05/18	118
Md Ayub	045380H	64	Male	Pyriform Sin	20.12.2017	T3N0M0	III	70Gy in 35	Fr	Nil	03/01/18	21/02/18	49	02/07/18	131
Ravindran	057356H	62	Male	Glottis	15.12.2017	T3N0M0	III	70Gy in 35	Fr	Weekly Cispl	26/12/17	15/02/18	51	16/05/18	90
Lestarly	050416H	57	Male	Pyriform Sin	26.12.2017	T4N2M0	IVA	70Gy in 35	Fr	3 weekly x 2	28/12/17	14/02/18	48	16/05/18	91
Mathias	085613H	52	Male	Tongue	01.01.2018	T4N1M0	IVA	70Gy in 35	Fr	3 weekly x 2	15/01/18	05/03/18	49	05/06/18	92
Rachel Vargh	047084H	48	Female	Oropharynx	17.01.2018	T2N2M0	IVA	70Gy in 35	Fr	3 weekly x 2	22/01/18	14/03/18	51	14/06/18	92
Lianhluna	100325H	58	Male	Supraglottis	31.01.2018	T3N0M0	III	70Gy in 35	Fr	Nimotuzumal	07/02/18	28/03/18	49	19/06/18	83
Sudhakar	711016D	30	Male	Oropharynx	14.02.2018	T3N1M0	III	70Gy in 35	Fr	3 weekly x 2	28/02/18	18/04/18	49	20/07/18	93
Gitapada Adl	118047H	74	Male	Oropharynx	21.02.2018	T4aN2bM0	IVA	70Gy in 35	Fr	Nil	01/03/18	19/04/18	49	06/07/18	78
Sunil Maji	117728H	63	Male	Pyriform Sin	14.03.2018	T1N0M0	I	70Gy in 35	Fr	Weekly Cispl	21/03/18	09/05/18	49	02/08/18	85
Pronoy Chak	916433G	47	Male	Oropharynx	25.07.2018	T4aN1M0	IVA	70Gy in 35	Fr	Weekly Cispl	03/08/17	27/09/17	55	07/03/18	161
Sivakumar	027473H	39	Male	Oropharynx	23.11.2017	T4N2M0	IVA								
Donbok Pass	590674G	50	Male	Pyriform Sin	12.03.2018	T3N2M0	IVA	70Gy in 35	Fr	3 weekly x 2	29/03/18	17/05/18	49		-43237
Norendra Bh	074933H	45	Male	Oropharynx	07.02.2018	T1N0M0	I	70Gy in 35	Fr	Nil	14/02/18	04/04/18	49		
Chattraman	090684H	58	Male	Soft Palate	24.01.2018	T4N0M0	IVA	70Gy in 35	Fr	Weekly Cispl	31/01/18	23/03/18	51		
Md Babar Isl	044028H	38	Male	Glottis	05.01.2018	T4N0M0	IVA								
Golap Das	074406H	52	Male	Pyriform Sin	26.12.2017	T3N0M0	III	70Gy in 35	Fr	3 weekly x 1	03/01/18	28/02/18	56		
Rizwan	023761H	73	Male	Pyriform Sin	24.11.2017	T3N2bM0	IVA	66Gy in 33	Fr	Nil	05/12/17	25/01/18	51		
Jafor Hossai	979870G	70	Male	Supraglottis	18.09.2017	T3N0M0	III	70Gy in 35	Fr	Nil	29/09/17	16/11/17	48		
Moktar Ahm	955489G	47	Male	Oropharynx	17.08.2017	T2N2M0	IVA	70Gy in 35	Fr	Weekly Cispl	28/08/17	13/10/17	46		

GTV CT	PET	PET1	Glucose	FDG Dose	Time to Scan	SUV primary	SUV node	PET2	Glucose	FDG Dose	Time to scan	SUV primary	SUV node	Scopy or Exa
42.7CC	10.2845	13.02.2017	73	229.8	78	14.74	7.85	18.07.2017	106	287.82	90	Nil	Nil	Normal
8CC	1.7417	13.03.2017	97	298.183	90	19.74	Nil	26.07.2017	110	272.61	80	Nil	Nl	Fullness, No l
9.3CC	0.5474	30.03.2017	103	244.2	67	11.42	Nil	12.09.2017	139	256.78	52	8.14	Nil	Residual
14.1CC	6.4195	13.03.2017	108	298.183	86	11.8	Nil	07.09.2017	125	256.41	67	Nil	Nil	Normal
117CC	37.1569	12.04.2017	115	280.2	112	21.13	4.01	07.09.2017	111	253.08	51	7.43	2.83	Normal
20.8CC	0.2985	17.03.2017	106	230.84	96	18.06	21.45	06.10.2017	100	222.4	55	3.6	Nil	Normal
28CC	7.7133	31.05.2017	116	235.32	47	13.07	Nil	15.01.2018	99	290.19	73	15.81	7.15	Residual
22.4CC	6.6351	01.06.2018	109	279.2	68	7.12	Nil	16.10.2017	99	239.04	55	5.03	Nil	Normal
11.8CC	3.3839	11.05.2017	80	251.3	56	10.6	Nil	23.10.2017	99	268.15	67	6.96	8.7	Normal
40CC	13.7348	1.05.2017	101	227.9	60	16.75	13.34	22.09.2017	103	256.04	58	4.27	Nil	Residual
12.3CC	3.0853	12.06.2017	124	224.74	47	18.08	17.45	26.10.2017	100	256.63	62	Nil	Nil	Normal
14.4CC	7.7133	10.07.2017	52	316.97	86	18.57	10.28	02.01.2018	159	320.2	87	Nil	Nil	Normal
12.7CC	1.44315	12.07.2017	98	364.54	60	10.38	Nil	21.12.2017	99	221.08	80	Nil	Nil	Normal
NA	NA	28.07.2017	121	319.532	60	Nil	18.31	19.03.2017	95	279.05	67	Nil	Nil	Normal
23.9CC	8.0617	16.08.2017	113	317.4	73	27.83	10.89	03.01.2018	104	291.7	67	3.84	Nil	Bulge
16.5CC	3.3175	17.08.2017	93	276.33	66	17.27	4.48	19.01.2018	90	304.66	72	7.49	Nil	Normal
NA	NA	28.08.2017	109	181.7	146	25.9	Nil	04.04.2018	157	237.61	54	Nil	Nil	Normal
14.1CC	8.0617	10.10.2017	128	227.2	140	18.42	11.5	10.01.2018	92	383.52	87	7.1	2.7	Normal
4.7CC	3.3175	18.10.2017	135	260.21	65	8.15	Nil	13.03.2018	101	296.6	70	Nil	Nil	Normal
10.4CC	1.045	20.10.2017	105	296.7	40	7.94	Nil	06.04.2018	109	282.38	43	Nil	Nil	Clinically Nor
43.4CC	2.936	27.10.2017	140	359.86	54	12.14	4.03	06.04.2018	151	225.84	72	6.45	Nil	Clinically Nor
50.3CC	13.6021	15.11.2017	117	363.18	110	Nil	36.87	06.04.2018	124	230.7	48	Nil	3.68	Normal
17.7CC	2.09	14.11.2017	109	244.92	82	14.99	16	11.05.2018	87	256.225	68	5.31	4.9	Normal
55.3CC	9.621	17.11.2017	105	255.4	90	17.03	12.88	17.04.2018	114	282.71	72	3.51	Nil	Normal
12.3CC	2.6208	24.11.2017	104	223.12	93	18.51	9.68	02.05.2018	102	282.08	45	3.32	2.72	Normal
78.9CC	36.5598	27.11.2017	104	256.61	110	17.97	6.74	09.04.2018	101	285.3	54	7.31	Nil	Clinically Nor
16.1CC	48.304	28.11.2017	130	267.76	130	9.57	9.12	04.05.2018	126	219.96	73	2.87	Nil	Normal
11.1CC	2.2393	29.11.2017	115	238.1	80	10.62	4.45	25.05.2018	107	268.62	58	Nil	Nil	Normal
31.7CC	4.7275	20.12.2017	91	273.57	75	22.85	2.83	02.07.2018	117	237	45	3.25	Nil	Normal
12.5CC	2.2891	15.12.2017	122	228.2	65	29.1	8.45	16.05.2018	135	224.1	80	3.79	Nil	Normal
21.4CC	7.6636	26.12.2017	109	225.7	116	24.02	23.72	16.05.2018	160	234.937	110	3.29		Normal
72.9CC	28.6971	01.01.2018	124	377.69	106	17.38	6.18	05.06.2018	102	259.5	93	4.51	Nil	Normal
47.6CC	23.8866	17.01.2018	105	263.68	98	11.55	21.1	14.06.2018	113	352.73	60	Nil	2.31	Normal
13.1CC	10.4006	31.01.2018	147	237.02	63	7.4	3.03	19.06.2018	183	311.25	64	Nil	Nil	Normal
27.9CC	9.0072	14.02.2018	100	269.73	78	34.82	6.73	20.07.2018	106	242.83	50	3.26	Nil	Normal
28.4CC	6.801	21.02.2018	94	219.07	102	26.13	3.48	06.07.2018	103	231.21	48	Nil	Nil	Clinically Nor
0.5CC	0.2488	14.03.2018	122	261.65	80	5.27	7.36	02.08.2018	112	225.09	57	4.12	Nil	Congested ec
56.1CC	20.4529	25.07.2017	96	321.49	150	44.35	28.26	07.03.2018	83	237.64	56	Nil	12.42	Normal

Biopsy	RECIST	T/B1	T/B2	T%1	T%2	Tvalue1	Tvalue2	SUVmax1	SUVmax2	SUVmean1	SUVmean2	Vol1	Vol2	TLG1
Nil	CR	4.4229	2.0583	38.0487	57.1961	6.4062	2.8784	16.8368	5.0326	9.9468	3.495	10.2845	15.012	102.2989
Nil	CR	4.6818	2.5321	38.3599	51.4854	7.5669	2.5969	19.7261	5.044	14.209	3.4364	1.7417	2.1398	29.74
Yes	PD	3.7465	3.4389	44.3994	42.8855	5.0697	3.4898	11.3872	8.1376	8.3357	4.685	0.5474	3.3839	4.563
Nil	PR	6.559	3.3595	32.27	43.3701	4.297	2.6693	11.803	6.1548	7.7016	3.5771	6.4195	10.2513	49.441
Nil	CR	6.4326	2.9389	32.5675	47.4635	7.0219	3.5241	21.5611	7.425	13.0287	5.2797	37.1569	2.4881	484.1093
Nil	CR	5.3988	2.846	39.693	47.393	8.515	2.091	21.453	4.41	17.317	2.6876	0.2985	5.3918	2.1912
yes	PD	4.4706	4.527	37.9313	38.1139	5.1578	6.0273	13.5979	15.8141	8.7768	10.0702	7.7133	4.5616	67.6989
Nil	CR	3.2961	1.9002	43.9681	65.4084	3.1313	3.0813	7.1219	4.71	4.5491	4.3058	6.6351	0.2985	30.1845
Nil	PR	5.6124	4.8301	35.0861	39.6051	3.5657	3.4469	10.1628	8.7032	6.1288	6.4322	3.3839	0.8293	20.7397
Nil	PR	4.1351	2.3186	39.0955	53.4745	5.8335	2.2977	14.9213	4.2969	9.3176	3.1127	13.7348	4.827	127.9768
Nil	CR	2.3819	3.6748	53.0946	41.4048	2.4853	1.9381	4.6809	3.1673	3.3195	2.5408	3.0853	12.4409	10.242
Nil	CR	4.0791	1.7574	39.5111	63.6462	7.3375	2.8591	18.5707	4.4922	12.7213	3.2838	7.7133	9.8532	98.1251
Nil	CR	5.3357	3.4077	36.75	43.4669	3.8155	2.1145	10.3824	4.8648	7.1387	2.8247	1.44315	3.6825	10.3022
Nil	CR													
Nil	PR	5.7834	3.2637	34.1322	48.6531	9.4996	3.0802	27.832	6.331	17.0394	5.1293	8.0617	0.3483	137.3673
Nil	CR	2.9263	3.0569	47.1082	47.0165	8.1367	3.5214	17.2723	7.4897	13.093	5.0868	3.3175	1.5924	43.4374
Nil	CR													
Nil	CR	13.7753	4.9837	26.6926	37.054	4.9178	2.6327	18.424	7.105	10.4524	4.4803	8.0617	2.2393	91.8941
Nil	CR	4.659	2.7528	39.4117	49.1046	3.2121	3.3846	8.1503	6.8927	5.9322	4.8552	3.3175	2.5877	6.3962
Nil	CR	3.499	2.0791	44.7465	56.7022	3.5534	2.2915	7.9412	4.0413	5.5002	2.821	1.045	22.2278	5.7479
Nil	SD	4.9999	3.9147	36.7154	40.3872	4.4557	2.6066	12.1359	6.4541	8.1467	4.1368	2.936	6.2204	23.919
Nil	SD	12.9377	3.533	26.9243	42.824	9.9267	2.576	36.869	6.4355	19.065	4.0604	13.6021	3.1848	259.333
Nil	SD	4.9692	3.0607	37.2852	46.6393	5.9666	2.4748	16.0027	5.3063	10.903	3.6163	2.09	1.7417	22.7882
Nil	CR	5.6938	2.9345	34.2921	46.5182	5.8414	1.9271	17.0343	4.1427	10.4295	2.8026	9.621	10.8485	100.3428
Nil	PR	6.692	3.4112	33.1299	45.5663	6.1327	2.5662	18.5111	5.6319	12.2444	4.0314	2.6208	0.845	32.091
Nil	SD	10.067	2.654	28.417	50.3826	5.105	3.6825	17.965	7.3091	11.001	5.2079	36.5598	2.1896	402.2032
Nil	SD	6.1829	2.9744	33.0149	46.2575	5.1215	2.285	15.5127	4.9398	7.4591	3.2338	48.304	7.2655	360.3085
Nil	CR	2.7154	3.5036	49.255	43.0637	5.2289	2.0626	10.616	4.7896	8.1102	2.8878	2.2393	2.9858	18.1618
Nil	CR	5.4673	3.0746	35.1415	50.5464	8.0298	3.1426	22.8501	6.217	15.3028	5.1127	4.7275	0.4976	72.3452
Nil	CR	5.0709	2.799	36.918	49.245	10.7443	2.6453	29.1031	5.3718	20.6601	3.5814	2.2891	1.3436	47.2938
Nil	CR	6.5638	7.3081	32.6312	31.5025	7.8377	1.536	24.019	4.8758	15.098	2.3656	7.6636	8.8081	115.7056
Yes/Normal	SD	5.1091	1.912	35.5678	61.4027	6.8826	2.8602	19.3506	4.6581	11.9911	3.4852	28.6971	2.4052	344.1118
Nil	CR	5.3112	1.9713	35.036	59.4187	7.3937	2.3026	21.1031	3.8753	13.4379	2.7336	23.8866	4.5285	320.9872
Nil	CR	4.7365	3.427	36.8918	42.8825	2.731	1.3926	7.4027	3.2475	4.9626	2.1027	10.4006	8.41	51.6147
Nil	CR	4.1111	3.7712	39.3396	42.3208	13.6981	2.9129	34.8202	6.8831	24.5257	4.4894	9.0072	1.891	220.9095
Nil	CR	7.4691	1.8903	31.3121	61.6818	8.8335	1.8405	28.2111	2.9255	17.4371	2.4029	6.801	1.6422	118.591
Yes	CR	7.4467	3.0395	36.4278	45.7279	2.6796	1.9139	7.3561	4.1854	6.076	2.4771	0.2488	9.7039	1.5118
Nil	PR	24.356	6.0317	24.1643	34.9731	11.7664	4.3429	48.6935	12.4178	29.2612	6.9781	20.4529	1.5924	598.4775

TLG2	Backgrd1	Backgrd2	PERCIST_SUL	PERCIST_TLG	PERCIST_SUV
52.468	2.2949	2.1412	PMR	PMR	PMR
7.3535	2.2272	1.8423	PMR	PMR	PMR
15.8539	2.1459	2.7896	PMR	PMD	SMD
36.67	2.541	2.13	PMR	PMR	PMR
13.137	2.6429	2.5208	PMR	PMR	PMR
14.627	2.02	1.7092	PMR	PMR	PMR
45.9372	2.6485	1.5155	SMD	SMD	SMD
1.2856	2.4681	2.0904	PMR	PMR	PMR
5.3348	2.4173	2.0971	PMD	PMD	SMD
15.0255	2.1385	1.9381	PMR	PMR	PMR
31.61	1.9278	2.4915	PMR	PMR	PMR
32.3562	2.1561	1.9892	CMR	CMR	CMR
10.4022	2.1402	2.1138	PMR	PMR	PMR
1.7868	2.6778	2.1001	PMR	PMR	PMR
8.1004	2.5705	2.0899	PMR	PMR	PMR
10.033	1.6954	2.2986	SMD	PMD	SMD
12.564	2.5939	2.3293	PMR	PMR	PMR
62.7053	2.9606	2.1003	CMR	CMR	CMR
25.7329	2.4146	1.8656	PMR	SMD	PMR
12.9321	2.3565	2.5853	PMR	PMR	PMR
6.2986	2.4288	2.4548	PMR	PMR	PMR
30.4045	2.1173	2.4358	PMR	PMR	PMR
3.4105	2.4907	2.6203	PMR	PMR	PMR
11.4074	2.191	2.2549	PMD	PMD	PMR
23.4956	2.5366	2.4579	PMR	PMR	PMR
8.6075	2.3582	2.3905	PMR	PMR	PMR
2.5443	2.3527	2.2946	PMD	PMD	PMR
4.8121	2.7608	2.2933	CMR	CMR	CMR
20.8366	1.5854	1.2597	PMR	PMR	PMR
8.3829	2.0448	2.2444	PMR	CMR	PMR
12.379	2.3069	2.1906	PMR	PMR	PMR
17.6842	2.1705	2.1323	CMR	CMR	PMR
8.4897	2.7469	2.4065	PMR	PMR	CMR
3.9461	2.072	1.8604	PMR	CMR	PMR
24.0377	2.1451	2.021	PMR	PMR	PMR
11.1123	2.014	1.8848	PMR	PMR	PMR

Name	Hospital Num	T/B1	T/B2	T%1	T%2	Tvalue1
Gunraj Steph	687582G	4.4229	2.0583	38.0487	57.1961	6.4062
Md Alauddin	762762G	4.6818	2.5321	38.3599	51.4854	7.5669
Tarrendro Di	550982G	3.7465	3.4389	44.3994	42.8855	5.0697
Kerson Sangr	793886G	6.559	3.3595	32.27	43.3701	4.297
Ranjan Sengu	832101G	6.4326	2.9389	32.5675	47.4635	7.0219
Abdul Gani	804236G	5.3988	2.846	39.693	47.393	8.515
Ishwar Prasa	877467G	4.4706	4.527	37.9313	38.1139	5.1578
Murali K	721444D	3.2961	1.9002	43.9681	65.4084	3.1313
Anoop Kuma	186878B	5.6124	4.8301	35.0861	39.6051	3.5657
Sylvanus Mas	553739G	4.1351	2.3186	39.0955	53.4745	5.8335
Pappi Thoma	890754G	2.3819	3.6748	53.0946	41.4048	2.4853
Mst Saleha	907200G	4.0791	1.7574	39.5111	63.6462	7.3375
Khokan Ghos	911441G	5.3357	3.4077	36.75	43.4669	3.8155
Ranjit Dey	948113G	5.7834	3.2637	34.1322	48.6531	9.4996
Mohammad	928837G	2.9263	3.0569	47.1082	47.0165	8.1367
Prodip Ranja	991110G	13.7753	4.9837	26.6926	37.054	4.9178
Subodh Adhi	978893G	4.659	2.7528	39.4117	49.1046	3.2121
Noel Stone	571785G	3.499	2.0791	44.7465	56.7022	3.5534
Harish Chanc	989849G	4.9999	3.9147	36.7154	40.3872	4.4557
Budha Bhatt	013254H	12.9377	3.533	26.9243	42.824	9.9267
Ranajit Kuma	024633H	4.9692	3.0607	37.2852	46.6393	5.9666
Medayil Alex	034350H	5.6938	2.9345	34.2921	46.5182	5.8414
Gnanaselvi	038589H	6.692	3.4112	33.1299	45.5663	6.1327
Kanniyappan	160439B	10.067	2.654	28.417	50.3826	5.105
Shaji Varghe	048746H	6.1829	2.9744	33.0149	46.2575	5.1215
Uttam Pal	031161H	2.7154	3.5036	49.255	43.0637	5.2289
Md Ayub	045380H	5.4673	3.0746	35.1415	50.5464	8.0298
Ravindran	057356H	5.0709	2.799	36.918	49.245	10.7443
Lestarly	050416H	6.5638	7.3081	32.6312	31.5025	7.8377
Mathias	085613H	5.1091	1.912	35.5678	61.4027	6.8826
Rachel Vargh	047084H	5.3112	1.9713	35.036	59.4187	7.3937
Lianhluna	100325H	4.7365	3.427	36.8918	42.8825	2.731
Sudhakar	711016D	4.1111	3.7712	39.3396	42.3208	13.6981
Gitapada Adh	118047H	7.4691	1.8903	31.3121	61.6818	8.8335
Sunil Maji	117728H	7.4467	3.0395	36.4278	45.7279	2.6796
Pronoy Chak	916433G	24.356	6.0317	24.1643	34.9731	11.7664

Tvalue2	SUVmax1	SUVmax2	SUVmean1	SUVmean2	Vol1	Vol2
2.8784	16.8368	5.0326	9.9468	3.495	10.2845	15.012
2.5969	19.7261	5.044	14.209	3.4364	1.7417	2.1398
3.4898	11.3872	8.1376	8.3357	4.685	0.5474	3.3839
2.6693	11.803	6.1548	7.7016	3.5771	6.4195	10.2513
3.5241	21.5611	7.425	13.0287	5.2797	37.1569	2.4881
2.091	21.453	4.41	17.317	2.6876	0.2985	5.3918
6.0273	13.5979	15.8141	8.7768	10.0702	7.7133	4.5616
3.0813	7.1219	4.71	4.5491	4.3058	6.6351	0.2985
3.4469	10.1628	8.7032	6.1288	6.4322	3.3839	0.8293
2.2977	14.9213	4.2969	9.3176	3.1127	13.7348	4.827
1.9381	4.6809	3.1673	3.3195	2.5408	3.0853	12.4409
2.8591	18.5707	4.4922	12.7213	3.2838	7.7133	9.8532
2.1145	10.3824	4.8648	7.1387	2.8247	1.44315	3.6825
3.0802	27.832	6.331	17.0394	5.1293	8.0617	0.3483
3.5214	17.2723	7.4897	13.093	5.0868	3.3175	1.5924
2.6327	18.424	7.105	10.4524	4.4803	8.0617	2.2393
3.3846	8.1503	6.8927	5.9322	4.8552	3.3175	2.5877
2.2915	7.9412	4.0413	5.5002	2.821	1.045	22.2278
2.6066	12.1359	6.4541	8.1467	4.1368	2.936	6.2204
2.576	36.869	6.4355	19.065	4.0604	13.6021	3.1848
2.4748	16.0027	5.3063	10.903	3.6163	2.09	1.7417
1.9271	17.0343	4.1427	10.4295	2.8026	9.621	10.8485
2.5662	18.5111	4.859	12.2444	3.4383	2.6208	1.7417
3.6825	17.965	7.3091	11.001	5.2079	36.5598	2.1896
2.285	15.5127	4.9398	7.4591	3.2338	48.304	7.2655
2.0626	10.616	4.7896	8.1102	2.8878	2.2393	2.9858
3.1426	22.8501	6.217	15.3028	5.1127	4.7275	0.4976
2.6453	29.1031	5.3718	20.6601	3.5814	2.2891	1.3436
1.536	24.019	4.8758	15.098	2.3656	7.6636	8.8081
2.8602	19.3506	4.6581	11.9911	3.4852	28.6971	2.4052
2.3026	21.1031	3.8753	13.4379	2.7336	23.8866	4.5285
1.3926	7.4027	3.2475	4.9626	2.1027	10.4006	8.41
2.9129	34.8202	6.8831	24.5257	4.4894	9.0072	1.891
1.8405	28.2111	2.9255	17.4371	2.4029	6.801	1.6422
1.9139	7.3561	4.1854	6.076	2.4771	0.2488	9.7039
4.3429	48.6935	12.4178	29.2612	6.9781	20.4529	1.5924

TLG1	TLG2	Backgrd1	Backgrd2	SUVmax	SUL	TLG
102.2989	52.468	2.2949	2.1412	16.8368	4.68	48.22
29.74	7.3535	2.2272	1.8423	19.7261	9.93	17.29
4.563	15.8539	2.1459	2.7896	11.3872	4.85	6.03
49.441	36.67	2.541	2.13	11.803	4.43	28.5
484.1093	13.137	2.6429	2.5208	21.5611	9.35	347.45
2.1912	14.627	2.02	1.7092	21.453	11.3	10.12
67.6989	45.9372	2.6485	1.5155	13.5979	6	46.35
30.1845	1.2856	2.4681	2.0904	7.1219	1.86	12.34
20.7397	5.3348	2.4173	2.0971	10.1628	2.19	1.45
127.9768	15.0255	2.1385	1.9381	14.9213	6.38	87.73
10.242	31.61	1.9278	2.4915	18.077	8.8	28.48
98.1251	32.3562	2.1561	1.9892	18.5707	4.21	32.49
10.3022	10.4022	2.1402	2.1138	10.3824	4.4	6.36
137.3673	1.7868	2.6778	2.1001	27.832	14.31	115.39
43.4374	8.1004	2.5705	2.0899	17.2723	8.26	27.42
91.8941	10.033	1.6954	2.2986	18.424	1.82	4.09
6.3962	12.564	2.5939	2.3293	8.1503	3.65	3.95
5.7479	62.7053	2.9606	2.1003	7.9412	2.38	2.49
23.919	25.7329	2.4146	1.8656	12.1359	6.36	18.69
259.333	12.9321	2.3565	2.5853	36.869	16.26	221.27
22.7882	6.2986	2.4288	2.4548	16.0027	7.95	16.61
100.3428	30.4045	2.1173	2.4358	17.0343	6.79	65.36
32.091	5.9886	2.4907	2.6203	18.5111	7.15	18.76
402.2032	11.4074	2.191	2.2549	17.965	8.27	302.52
360.3085	23.4956	2.5366	2.4579	15.5127	4.78	230.93
18.1618	8.6075	2.3582	2.3905	10.616	5.76	12.89
72.3452	2.5443	2.3527	2.2946	22.8501	10	47.28
47.2938	4.8121	2.7608	2.2933	29.1031	17.12	39.21
115.7056	20.8366	1.5854	1.2597	24.019	12.06	92.48
344.1118	8.3829	2.0448	2.2444	19.3506	10.27	294.78
320.9872	12.379	2.3069	2.1906	21.1031	8.22	196.38
51.6147	17.6842	2.1705	2.1323	7.4027	3.36	35.01
220.9095	8.4897	2.7469	2.4065	34.8202	17.08	153.87
118.591	3.9461	2.072	1.8604	28.2111	13.58	86.87
1.5118	24.0377	2.1451	2.021	7.3561	4.19	1.04
598.4775	11.1123	2.014	1.8848	48.6935	23.33	477.24

PERCIST SUL	PERCIST TLG	PERCIST SUVMAX
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMD	SMD
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMR	PMR
SMD	SMD	SMD
PMR	PMR	PMR
PMR	PMD	SMD
PMR	PMR	PMR
PMR	PMR	PMR
CMR	CMR	CMR
PMR	PMR	PMR
PMR	CMR	PMR
PMR	PMR	PMR
SMD	PMD	SMD
PMR	PMD	PMR
CMR	CMR	CMR
PMR	SMD	PMR
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMR	PMR
PMR	PMR	PMR
CMR	CMR	CMR
PMR	PMR	PMR
PMR	CMR	PMR
CMR	CMR	CMR
CMR	CMR	PMR
CMR	CMR	CMR
PMR	CMR	PMR
PMR	PMD	PMR
CMR	CMR	CMR